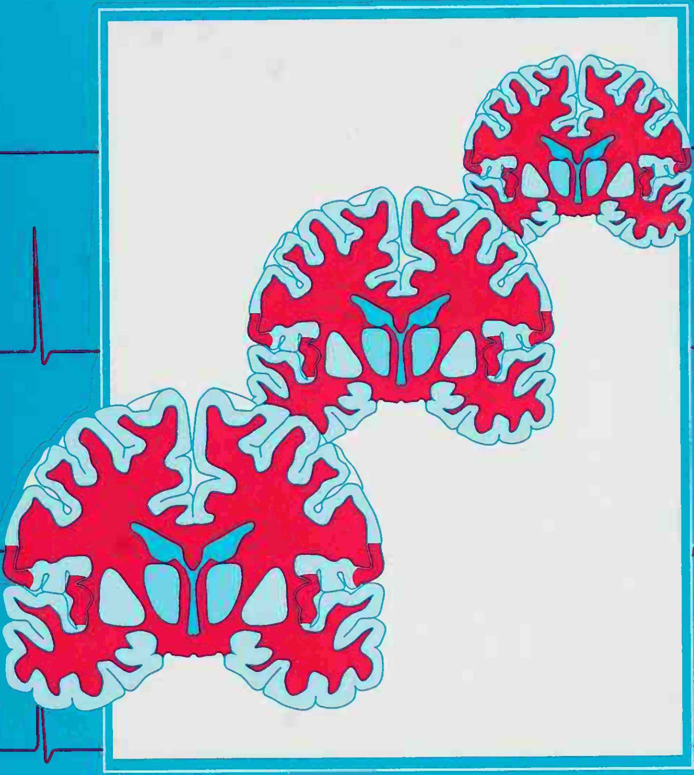
Neurobiology

Molecules, Cells, and Systems



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Molecules, Cells, and Systems

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NEUROBIOLOGY

Molecules, Cells, and Systems

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To Karen and David

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Preface

Neurobiology is a very broad and diverse subject, as instructors of neurobiology know well and students will soon find out. This fact encourages an encyclopedic approach to textbook writing in which many topics are covered, and some excellent survey texts are available that take this approach to the field. The approach I have taken in writing this introductory textbook of neurobiology is different, however. Instead of a broad survey, I have selected a subset of topics within neurobiology, where explanations at cellular, molecular, and neural-circuit levels can be provided with some rigor. The book emphasizes basic properties of nerve cells and neural circuits—knowledge that will provide a foundation for further learning. For each topic, I have limited the coverage to a few specific examples, which were chosen with care to illustrate fundamentals of nervous system function. My intent is that these examples will provide a framework that individual instructors can then supplement in topic areas that suit their interests and the purposes of their courses.

The figures and diagrams in the book also require some comment. It seems to be common practice in undergraduate neurobiology texts that figures are taken directly or slightly modified from original research articles. Beginners simply lack the experience to sort through the information to extract important principles and are often confused by figures whose original purpose was to communicate as much information as possible in a limited space to experienced research workers. In this book, figures have been kept simple. Most consist of schematic drawings, tailored to illustrate a particular point. Although such figures may appear primitive to research neurobiologists, I know from experience that students find them more accessible and comprehensible. I also hope that students will find the book as a whole both accessible and comprehensible.

Gary G. Matthews

Acknowledgments

I would like to express my thanks to my colleagues in the Department of Neurobiology and Behavior at the State University of New York at Stony Brook—one of the best and most interactive scientific environments for neurobiology around. Since 1981, I have learned much, both formally and informally, from my scientific colleagues in the department. I would never have attempted this book without that experience. Of course, if you find any mistakes in this book, it's all *their* fault.

Special thanks go to Joe Fetcho and Peter Shizgal, who read the entire manuscript with care and made many valuable suggestions. The commendation for most biting comment is awarded to Dr. Fetcho, for pointing out that "highest vertebrate = Himalayan Snow Goose."

The approach to instruction taken in this book is inspired by my own predoctoral and postdoctoral teachers. I acknowledge my long-term debt to the following individuals: Randy Gallistel of the University of Pennsylvania (now at UCLA); Warren Wickelgren, Bob Martin, and Bill Betz at the University of Colorado Medical School; and at Stanford University, Denis Baylor and John Nicholls (now at the University of Basel, Switzerland).

The most important acknowledgment is to my wife Karen, whose support and tolerance made the writing possible.

PART I

Introduction to Neurobiology

In the first two chapters of this textbook, our goal is to provide an overview of nervous system function and organization. This overview will serve as a framework that will be fleshed out as students learn more about the details of neurobiology in subsequent parts of the book.

Chapter 1 has the dual purpose of introducing the signaling functions of the nervous system and describing some of the very different scientific approaches that can be used to study it. Neurobiology represents a fair cross section of its parent science, biology, and many different levels of scientific analysis can be employed in neurobiology, ranging from studies of intact organisms to fundamentals of gene expression. Some of those levels of analysis will be illustrated in chapter 1.

Chapter 2 focuses on the overall structural organization of the mammalian central nervous system. This organization will be examined both in the context of phylogenetic evolution and in terms of embryological development. In both processes, neural organization proceeds from simpler to more complex forms.

After this two-chapter introduction to neurobiology and neural organization, Part 2 provides some specific details about neuronal communication.

1

An Overview of Neurobiology

This is a book about the nervous system, the master control system that coordinates the actions of the other organ systems that make up the organism. To understand how the nervous system carries out this task, students of neurobiology must master a wide variety of facts about the anatomy, cell biology, and biochemistry of the nervous system. This rapidly increasing body of information provides the foundation required for appreciation of how the nervous system as a whole works.

It is perhaps equally important that students learn how neurobiologists go about studying the nervous system and gathering new information. Although our knowledge of the nervous system is impressive, the amount we do not know is also vast. Recognizing the scientific tools that neurobiologists use in the course of their research will help students keep pace with new advances in our understanding of the brain. For that reason, we will begin by examining some of the different approaches neurobiologists use to study the nervous system. In the process, we will also begin to see how the nervous system is organized and what kinds of cellular events underlie its functioning.

As a scientific discipline, neurobiology differs from most other specialties within the realm of biological science. Molecular biology, for example, is a field organized around a particular set of techniques and methods—a particular way of asking and answering scientific questions. A molecular biologist who works on yeast cells can probably understand the work of her fellow molecular biologist who works on mammalian cells in the lab next door; the details of their respective systems may differ, but both scientists will share common language and common approaches to their work. The same cannot be said of neurobiology, however. A neurobiologist may be trained to be a biochemist, a physiologist, an anatomist, a behaviorist, or a molecular biologist. The common thread that unites neurobiologists of all scientific persuasions is that they all work on the nervous system—the most complex and mysterious of organ systems. Given the many scientific approaches that can be taken to the study of the nervous system, students studying neurobiology (and research neurobiologists, too) face the difficult task of mastering a wide range of information about nerve cells and how they interact.

Like other organs in the body, the nervous system is made up of cells, including the nerve cells themselves, called **neurons**, and their supporting and sustaining cells, called **glial cells.** Much of neurobiology focuses on understanding how the cells of the nervous system are specialized to carry out the transmission and processing of information. The first major subdivision of this book (Part 2), beginning with chapter 3, will deal with these cellular aspects of neurobiology.

The next two major subdivisions (Parts 3 and 4) cover neuronal circuits in the nervous system that mediate two of the important functions of the nervous system: formulating a motor response that makes sense for the organism in a particular context (motor systems; Part 3), and gathering information about the environment (sensory systems; Part 4). In addition to the properties of the individual neurons, the proper processing of both motor and sensory information depends on the specificity of connections among the numerous cells that make up the nervous system. Knowing the location where a particular nerve cell sends its outputs and the source of its inputs is crucial in understanding the cell's role in neural information processing. For this reason, neuroanatomy represents an important aspect of neurobiology. In each neural system described in this textbook, we will consider how that system is organized anatomically.

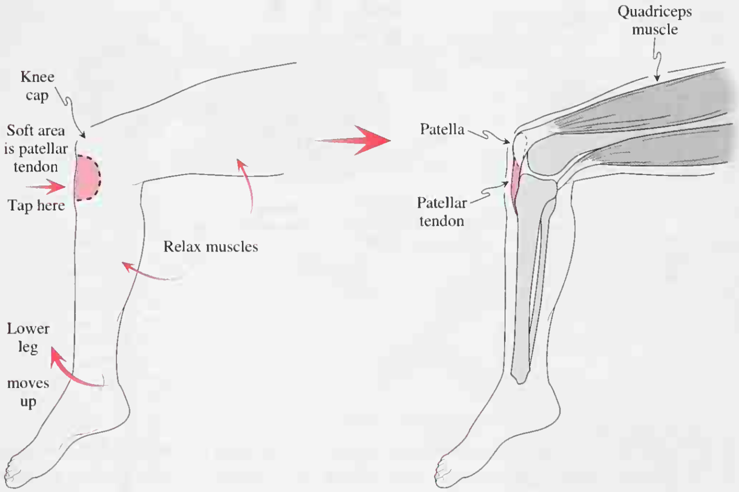
Finally, in Part 5, we will consider alterations in the connections among neurons on the basis of experience. These modifications occur during neural development in the embryo and during learning in the adult animal.

THE PATELLAR REFLEX: AN EXAMPLE OF NERVOUS SYSTEM FUNCTION

Rather than continue to speak abstractly about neurobiology and the various scientific approaches to study of the nervous system, let's consider a simple example, which we will examine from different viewpoints. The simple behavior we will analyze is perhaps the best-known example of a neural reflex—the knee-jerk reflex, which is more properly called the **patellar stretch reflex.** You can easily demonstrate this reflex on yourself as shown in Figure 1.1. While seated, cross one leg over the other and relax your thigh muscles. Find the patellar tendon (the soft spot between the knee cap and the head of the lower leg bone) and give it a sharp tap with the side of your open hand. (It helps to rest your other hand on the top of the thigh so that you can feel what happens to the quadriceps muscle at the front of the thigh.) If you are successful, the tap to the patellar tendon will be followed by extension of the lower leg, seemingly acting on its own. With your free hand resting on the front of the thigh, however, you can feel the twitch of the quadriceps muscle that causes the involuntary extension of the knee joint and the upward jerk of the lower leg.

The knee-jerk reflex is not only a well-known example of a reflex, but also one of the very simplest in terms of the neuronal connections that give rise to it. Figure 1.2 diagrams the neural circuitry underlying the patellar reflex. The tap to the patellar tendon pulls down on the knee cap (patella), which in turn stretches the quadriceps muscle. The nervous system then comes into play. Specialized nerve cells (**sensory neurons**) sense the stretch of the muscle and send a signal to the nervous system that the muscle length has

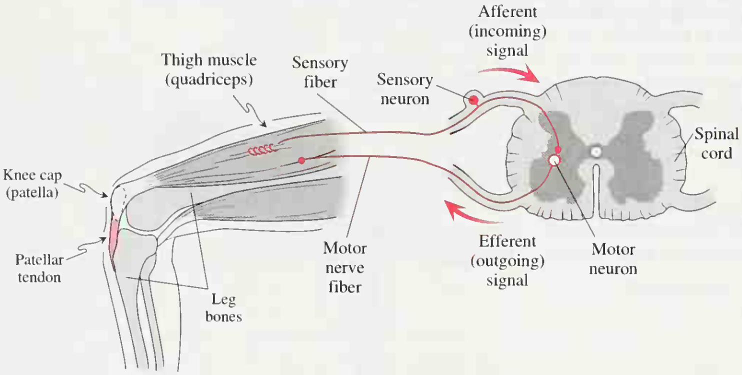
Figure 1.1
The patellar reflex. The goal is to passively stretch the relaxed quadriceps muscle at the front of the thigh by tapping sharply on the tendon attached to the bottom of the knee cap. Take a seat in such a way that the thigh is approximately horizontal, the foot is off the floor, and the muscles of the leg are relaxed. Next, deliver a sharp tap to the patellar tendon. A rubber reflex hammer can be used, or you can use either the side of your open hand or the ends of your bunched fingers. If you are successful, the lower leg will jerk upward (hence, the name knee-jerk reflex). You can also feel and see the reflexive contraction of the quadriceps muscle.



increased. This signal is received by other neurons, called **motor neurons**, that are located within the spinal cord (see Fig. 1.2). The motor neurons command the quadriceps muscle to contract, which produces the reflexive extension of the knee joint.

This simple reflex loop embodies many of the general properties that characterize the operation of the nervous system. A sensory stimulus (muscle stretch) is detected, the signal is transmitted rapidly over a long distance (to and from the spinal cord), and the information is focally and specifically directed to appropriate target neurons (the quadriceps motor neurons). The sensory pathway, which carries information into the nervous system, is called the **afferent pathway**; the motor output constitutes the **efferent pathway**. Much of the nervous system's activity relates to processing the afferent sensory information received from the body and then making the proper connections with the efferent pathways to ensure that an appropriate response occurs.

Figure 1.2
A schematic representation of the patellar reflex. The sensory neuron is activated by stretching the thigh muscle. The incoming (afferent) signal is carried to the spinal cord along the nerve fiber of the sensory neuron. In the spinal cord, the sensory neuron activates motor neurons, which in turn send outgoing (efferent) signals along the nerve back to the thigh muscle, causing it to contract.



Anatomy of the patellar reflex

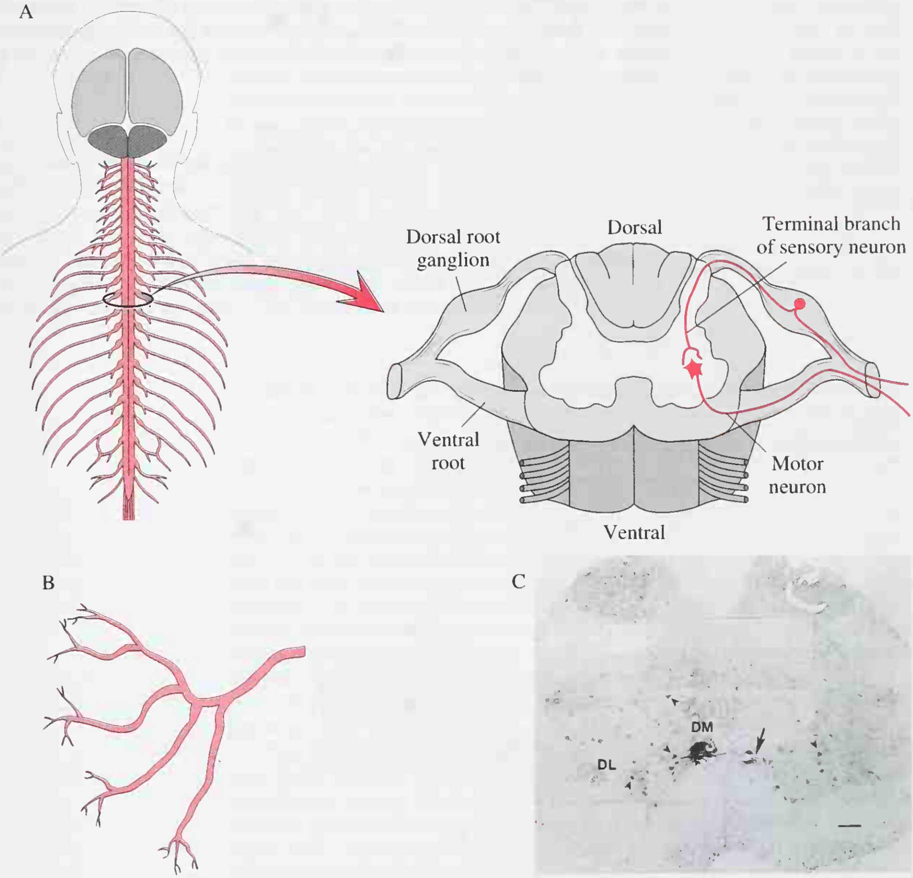
To draw the diagram shown in Figure 1.2, we must know where the neurons in the loop are located and where they project—that is, the relevant neuroanatomy. The cell bodies of the sensory neurons in the patellar reflex are located just outside the spinal column in the **dorsal root ganglion**. Each vertebral segment has two dorsal root ganglia, one on each side of the spinal cord (Fig. 1.3A). Each dorsal root ganglion in the chain of ganglia paralleling the spinal column provides the sensory innervation for a particular region of the body. The ganglia contain the cell bodies of a variety of different kinds of sensory neurons. In addition to those carrying sensory signals from muscles, there are sensory neurons that signal information about touch, pressure, pain, temperature, and so on.

In the patellar reflex, each sensory cell that innervates the quadriceps muscle gives rise to a single, thin projection. This projection exits the dorsal root ganglion and then bifurcates, sending one long process through the spinal nerve to the muscle and another long process via the **dorsal root** into the spinal cord. Once inside the spinal cord, the sensory nerve fiber branches profusely (Fig. 1.3B) and makes contact with numerous spinal cord neurons.

Among the spinal cord neurons contacted by the sensory neuron are the motor neurons that control the quadriceps muscle. The cell bodies of these motor neurons are located in the ventral part of the spinal cord. A group of

Figure 1.3

The organization of sensory and motor neurons in the spinal cord. (A) At each vertebra in the spinal column, a pair of spinal nerves exits, one for each side of the body. At the spinal cord, the nerve splits into dorsal and ventral branches (called **roots**), with the sensory nerve fibers residing in the dorsal root and the motor nerve fibers found in the ventral root. (B) In the spinal cord, sensory nerve fibers branch profusely. (C) The motor neurons, whose axons exit the spinal cord in the ventral root, are located in the ventral part of the spinal cord.



(C) Reproduced by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc., from Peshori KR, et al. Differences in the connectivity of rat pudendal motor nuclei as revealed by retrograde transneuronal transport of wheat germ agglutinin. J Comp Neurol 1995;353:119–128.

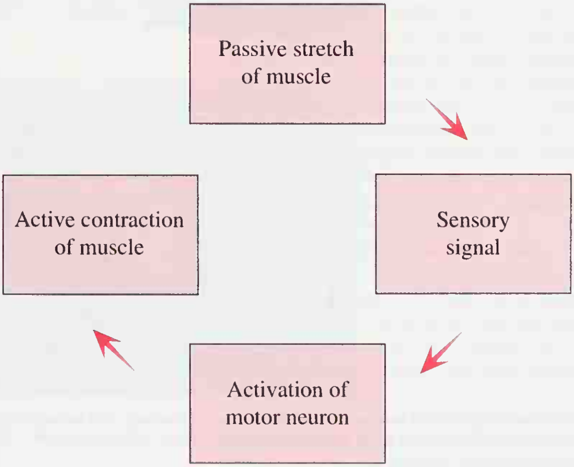
motor neurons that control a particular muscle is shown in Figure 1.3C. The long, thin output process of each motor neuron, the **axon**, exits the spinal cord via the **ventral root** and joins the spinal nerve to make the journey to the quadriceps muscle. Thus, the spinal nerve exiting each spinal segment consists of a mixed nerve carrying both afferent sensory fibers and efferent motor fibers.

In a simple case such as the patellar reflex, the neuroanatomy may seem relatively trivial. In a complex structure like the mammalian brain, which is characterized by complicated interconnections among neurons in neighboring and distant parts of the brain, the anatomy of the neural pathways is often not so straightforward, however. Chapter 2 provides an overview of brain organization.

Cellular signals involved in the patellar reflex

If the nervous system is to carry out its mission, signals must be sent and received among neurons. Even a simple reflex arc like the patellar reflex involves several different signals (Fig. 1.4). The stretch of the quadriceps muscle is sensed by the sensory neurons, which must produce a signal that propagates along the long, thin sensory nerve fibers into the central nervous system. At the junction where connection occurs between the sensory neurons and the motor neurons controlling the quadriceps muscle, the signal

Figure 1.4
A block diagram of the sequence of events in the stretch reflex.


Passive stretch of muscle
Sensory signal
Activation of motor neuron
Active contraction of muscle

that a stretch of the muscle has taken place must then be transmitted to the motor neurons. The point of contact—where signals are transmitted from one neuron to another—is called a **synapse**. The resulting activation of the motor neurons generates a message that is sent back along the nerve supplying the quadriceps muscle, where a second junction occurs between the ending of the motor nerve fibers and their target cells, the muscle cells of the quadriceps muscle. This synapse between a motor neuron and a muscle cell is called the **neuromuscular junction.**

The nervous system relies on two fundamental types of signals: electrical and chemical. Both types are observed in the patellar reflex. First, we will consider the long-distance signal sent up the sensory nerve fibers in response to muscle stretch and down the motor nerve fibers to command reflexive contraction of the muscle. This signal, called the **action potential,** is one of the fundamental electrical signals of the nervous system. Next, we will examine the transmission of information from one cell to another at the two synapses in the reflex: the connection between the sensory and motor neurons in the spinal cord, and the connection between the motor neurons and the muscle cells in the muscle. The transmission of information at these synapses involves the release of a chemical messenger, a **neurotransmitter**, which subsequently produces an electrical change in the target cell.

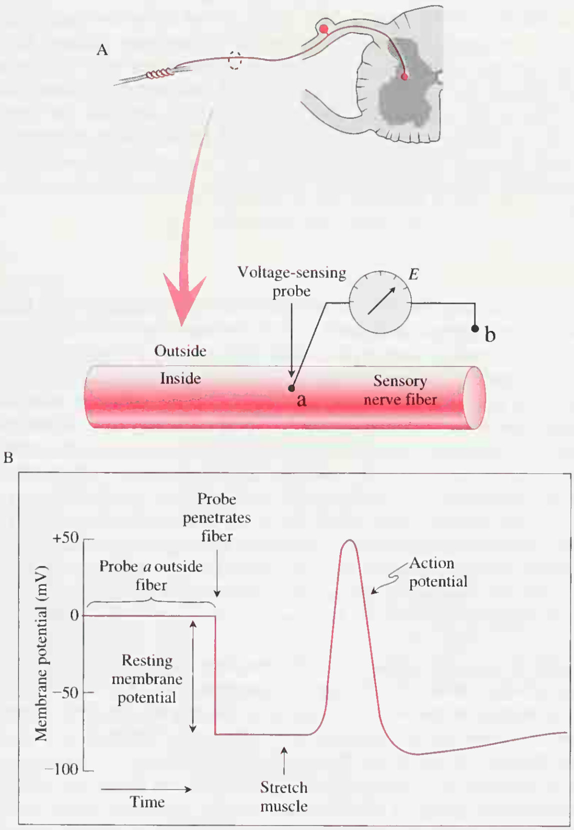
The action potential

The nervous system must be able to transmit information rapidly over fairly long distances. For example, information must be passed over the substantial distance from an elephant's toe to its spinal cord or from a giraffe's brain to the end of its spinal cord. To satisfy this requirement, neurons utilize changes in the electrical gradient across the cell membrane to generate electrical signals, which are then conducted rapidly along the long, thin fibers that make up the transmission paths of both the peripheral nerves and the central nervous system. Like all other cells, neurons have an electrical voltage difference between the inside and outside of the cell, with the inside being more negative than the outside. (The origin of this voltage difference, which is known as the **membrane potential,** is described in chapter 4.) Although this transmembrane voltage is small—typically less than one-tenth of a volt—it is central to the functioning of the nervous system. Information is transmitted and processed by neurons in the form of changes in the membrane potential.

What kind of electrical signal carries the message along the sensory nerve fiber in the patellar reflex? To answer this question, we must measure the membrane potential of the sensory neuron by placing an ultrafine voltage-sensing probe, called an intracellular microelectrode, inside the sensory nerve fiber. Figure 1.5 illustrates this kind of experiment. A voltmeter is connected to measure the voltage difference between the tip of the intracellular microelectrode (point *a* in the figure) and a reference point in the extracellular space (point *b*). When the microelectrode is located outside the sensory neuron, points *a* and *b* both lie in the extracellular space, and

Figure 1.5

Recording the action potential in the nerve fiber of the sensory neuron in the patellar stretch reflex. (A) A diagram of the recording configuration. A very fine voltage-sensing probe *a* is inserted into the sensory nerve fiber. The voltage difference between the inside and the outside of the nerve fiber is measured by a voltmeter that registers the electric field across the membrane, *E*. (B) When the probe penetrates the fiber, it measures the resting membrane potential of the nerve fiber. When the sensory neuron is activated by stretching the muscle, an action potential occurs, which is recorded as a rapid shift in the membrane potential of the sensory nerve fiber.



the voltmeter finds no voltage difference (see Fig. 1.5B). When the tip of the probe is inserted inside the sensory neuron, however, the voltmeter measures an electrical potential between points *a* and *b,* caused by the voltage difference between the inside and the outside of the neuron—that is, the membrane potential of the neuron. As shown in Figure 1.5B, the inside of the sensory nerve fiber is negative with respect to the outside by approximately 70/1000 of a volt (1 millivolt, abbreviated mV, equals 1/1000 of a volt). Because the potential outside the cell is defined as zero and the inside is negative with respect to the outside, the membrane potential is equal to roughly −70 mV.

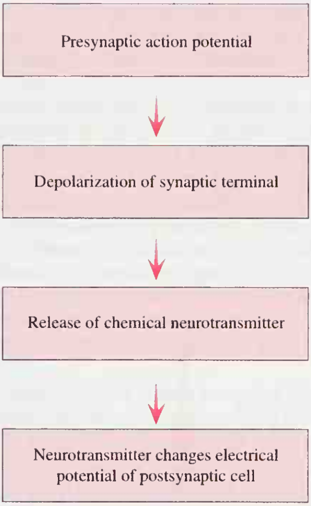
As long as the sensory neuron is not stimulated by stretching of the muscle, the membrane potential remains constant at this resting value. For this reason, the unstimulated membrane potential is known as the **resting potential** of the cell. When the muscle is stretched, however, the membrane potential of the sensory neuron undergoes a dramatic change, as shown in Figure 1.5B. After a delay that depends on the distance of recording point *a* from the muscle, a rapid and transient change occurs in the membrane potential. The voltage moves in the positive direction, transiently reverses its sign for a brief period, and then returns to the resting negative level. This transient jump in membrane potential, called the **action potential**, represents the long-distance signal used to carry information in the nervous system.

If we recorded the membrane potential at various points along the length of the sensory nerve fiber, we would find that the action potential travels from the sensory endings in the muscle to the synaptic endings of the sensory neuron in the spinal cord. The speed at which it moves is not very fast compared with the speed of electricity in a wire, but it is still quite fast for a biological process. For the stretch-sensitive sensory neurons involved in the patellar reflex, for example, the action potential travels at 50–100 m/s along the nerve fiber. Thus, the signal reaches the spinal cord in approximately 10/1000 to 20/1000 of a second (10–20 ms). A similar action potential is noted in the axon of the motor neuron when the contraction command is sent from the spinal cord to the quadriceps muscle in the return loop of the patellar reflex. A major focus for Part 2 of this book, beginning with chapter 3, will be to understand the electrical and chemical principles that underlie the generation of the action potential.

Synaptic transmission

As noted above, the action potential is the electrical signal that travels along the sensory and motor nerve fibers during the patellar reflex. What happens when the signal reaches the end of the neuron and must be transmitted to the next cell in the loop? In the patellar reflex, signals must be relayed from one cell to another at two synapses: the synapse between the sensory neuron and the motor neuron in the spinal cord, and the synapse between the motor neuron and the muscle cells of the quadriceps muscle. There are two general classes of synapses: **electrical synapses** and **chemical synapses.** In both types, specialized membrane structures are found at the point where the input cell (called the **presynaptic cell**) comes into contact with the receiving cell (called the **postsynaptic cell**). In the patellar reflex, both the synapse between the sensory neuron and the motor neuron and the synapse between the motor neuron and the muscle cells are chemical synapses.

Figure 1.6
A block diagram of the sequence of events involved in the release of chemical neurotransmitter from the synaptic terminal.


Presynaptic action potential
Depolarization of synaptic terminal
Release of chemical neurotransmitter
Neurotransmitter changes electrical potential of postsynaptic cell

The sequence of events during transmission at a chemical synapse is summarized in Figure 1.6. In this type of synaptic transmission, an action potential in the presynaptic cell causes it to release a chemical substance, called a **neurotransmitter**, that diffuses through the extracellular space at the point of synaptic contact and changes the membrane potential of the postsynaptic target cell. Transmission is simpler at an electrical synapse, and the change in membrane voltage during the action potential in the presynaptic cell spreads directly to the postsynaptic cell without the action of any intermediary chemical signal. Understanding the mechanisms of synaptic transmission will be the other major focus of Part 2.

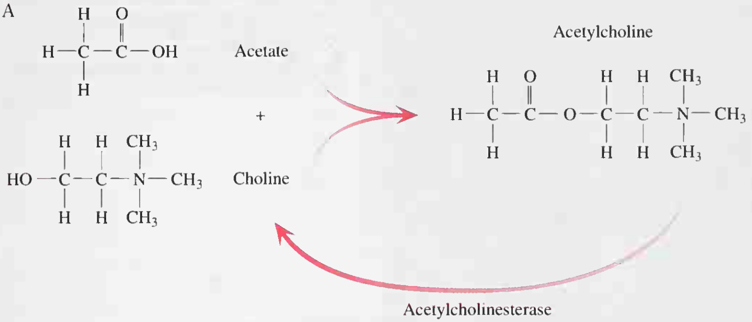
Molecular view of the patellar reflex

To this point, we have examined the patellar reflex from an exclusively cellular viewpoint—both in terms of the anatomy and in terms of the physiological signals—without paying much attention to subcellular mechanisms that give rise to the cellular events. Like all other cells, neurons are complex assemblies of molecular components. An important aspect of neurobiology is understanding how the properties of these molecular components contribute to nervous system function. In the patellar reflex, for example, many different molecules influence the various components of signal transmission. To illustrate the molecular approach to neural function, we will focus on the transmission of information at the synapse between the motor neurons and the muscle cells, called the **neuromuscular junction.**

As described in Figure 1.6, an action potential arriving at a synaptic terminal causes the release of a chemical neurotransmitter substance, which in turn alters the electrical behavior of the postsynaptic cell. At any synaptic junction in the nervous system, the chemical identity of the neurotransmitter released at that synapse is an important piece of molecular information. Indeed, a great deal of neurobiological research is devoted to specifying which neurotransmitters are released at which synapses in a neuronal circuit, because such information helps to explain how the circuit works. At the neuromuscular junction, the neurotransmitter released from the synaptic terminals of the motor neurons is a simple organic molecule, **acetylcholine,** the chemical structure of which is shown in Figure 1.7A. Acetylcholine (abbreviated ACh) is manufactured inside the motor neuron synaptic terminal by the chemical combination of acetate and choline, a reaction that is catalyzed by the enzyme **choline acetyltransferase** (see Fig. 1.7A).

A common piece of neurochemical evidence that a particular neuron uses a specific neurotransmitter is the presence of the synthetic enzyme for the neurotransmitter inside that neuron. Thus, staining neural tissue

Figure 1.7
Acetylcholine is a well-studied neurotransmitter in the nervous system that is released from the synaptic terminals of the motor neurons at the neuromuscular junction. (A) Acetylcholine is synthesized by the enzyme choline acetyltransferase (ChAT) from the precursors choline and acetate. After finishing its job as a neurotransmitter, acetylcholine is inactivated by being split into choline and acetate by the enzyme acetylcholinesterase (AChase).



to reveal choline acetyltransferase can establish which neurons in a circuit are likely to release ACh as a neurotransmitter. The presence of choline acetyltransferase inside a neuron can be detected with chemical probes, as illustrated by the stained neurons in Figure 1.7B. Such neurons are called **cholinergic neurons**, of which vertebrate motor neurons are the premier example.

After a chemical neurotransmitter has been released from the synaptic terminal, its action must be terminated in some way. Otherwise, the continued presence of the neurotransmitter in the extracellular space would continually activate the postsynaptic cell. Consequently, a neurotransmitter released by later action potentials arriving at the synaptic terminal would not be able to affect the postsynaptic cell. The action of a neurotransmitter can be terminated in either of two ways:

- Removal of the transmitter molecules from the extracellular space by having them be taken up by surrounding glial cells and neurons (including the presynaptic terminal that originally released the transmitter).
- Chemical degradation of the neurotransmitter molecules into inactive substances.

At the neuromuscular junction, the latter mechanism is used to inactivate ACh released from the synaptic terminals of the motor neurons. The extracellular space between the motor nerve terminals and the postsynaptic muscle cell contains an enzyme that destroys ACh (see Fig. 1.7A). Because this destructive enzyme works by cleaving the ester bond between acetate

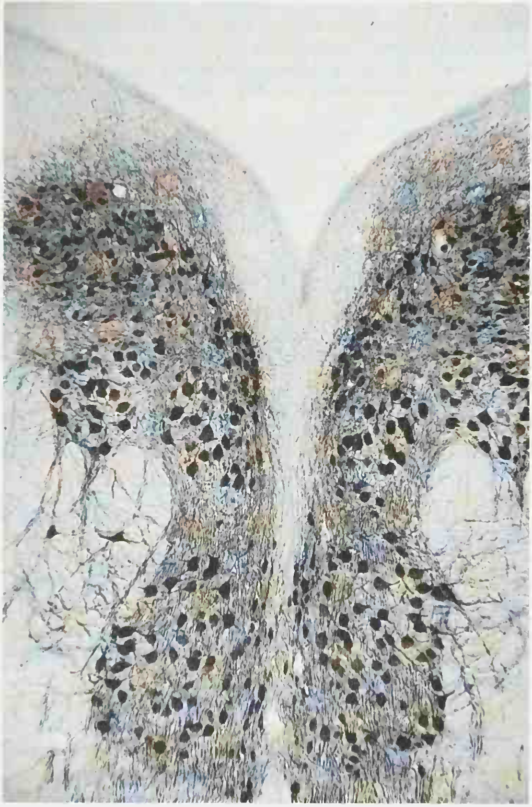


Figure 1.7 (continued)
(B) Choline acetyltransferase can be used as a marker to define which neurons in the nervous system are likely to employ ACh as a neurotransmitter. The cluster of neurons shown here has been labeled to reveal ChAT in the oculomotor nucleus, which controls eye movements.

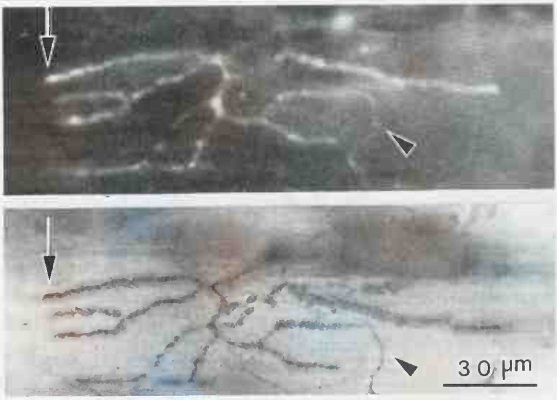
(B) Courtesy of J. T. Erichsen of the University of Wales.

and choline, it is called **acetylcholinesterase** (abbreviated AChase). Just as the synthetic enzyme choline acetyl transferase can be used as a marker for synapses at which ACh functions as the neurotransmitter, AChase in the extracellular space at a synaptic junction can be used to detect cholinergic synapses. AChase staining at the neuromuscular junction marks the postsynaptic muscle cell at the precise location where the nerve terminal is located (Fig. 1.7C). It can also be used to mark ACh synapses at other places in the nervous system, such as within the group of neurons shown in Figure 1.7D.

The goal of synaptic transmission is modification of the electrical prop-

Figure 1.7 (continued)
(C) The postsynaptic muscle cell at the neuromuscular junction contains AChase. The nerve terminal is shown in the upper picture and the pattern of AChase is shown in the same muscle cell in the lower picture.

(C) Reproduced by permission from Chen L, Ko C-P. Extension of synaptic extracellular matrix during nerve terminal sprouting in living frog neuromuscular junctions. J Neurosci 1994;14: 796–808.



C

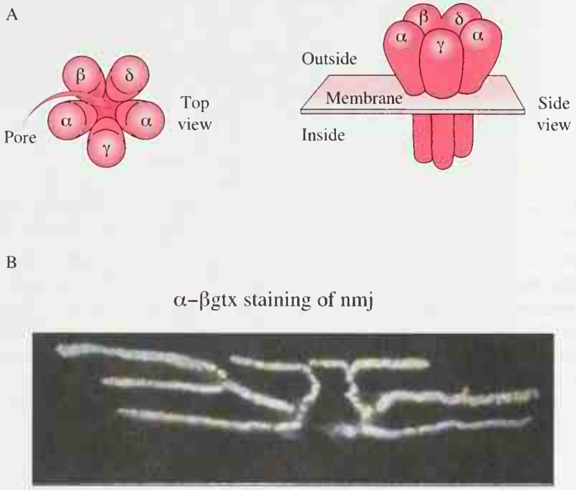
erties of the postsynaptic cell by the neurotransmitter released from the presynaptic cell. For this action to occur, the postsynaptic cell must detect the presence of the neurotransmitter in the extracellular space and respond appropriately. This detection is accomplished by specialized postsynaptic **neurotransmitter receptors**—transmembrane protein molecules that are inserted into the postsynaptic membrane at the point where the synaptic terminal of the presynaptic cell makes contact. The extracellular portion of the receptor molecule contains a binding pocket into which a molecule of neurotransmitter fits precisely. When the binding site is

Figure 1.7 (continued)
(D) Similarly, AChase can be used to label cholinergic synapses in other parts of the nervous system. The neurons shown here are a group of cholinergic motor neurons within a ganglion of the autonomic nervous system.

(D) Courtesy of J. T. Erichsen of the University of Wales.

D

Figure 1.8
The acetylcholine receptor mediates the postsynaptic response to the neurotransmitter acetylcholine. (A) A diagram of the structure of the ACh receptor. The protein acts as a transmembrane ion channel, formed from the combination of five subunits: two alpha subunits, and one subunit each of beta, gamma, and delta. When two molecules of ACh bind to the receptor (one to each alpha subunit), the ion channel opens and allows ions to traverse the membrane. (B) The location of the ACh receptors at the neuromuscular junction. The receptors have been labeled with a toxin from snake venom, alpha-bungarotoxin, which binds to the ACh-binding sites of the receptor.



(B) Reproduced by permission from Chen L, Ko C-P. Extension of synaptic extracellular matrix during nerve terminal sprouting in living frog neuromuscular junctions. J Neurosci 1994;14:796–808.

occupied, the receptor protein becomes activated, triggering a postsynaptic response.

Because the binding site will accept only a particular neurotransmitter substance, many different types of postsynaptic receptor molecules are found in the nervous system, providing specific detectors for the many different types of neurotransmitters. At the neuromuscular junction, for example, the postsynaptic membrane of the muscle cell contains large numbers of ACh receptors that detect the ACh released from the terminals of the motor neurons. The ACh receptors are formed from the aggregation of five protein subunits, as shown in Figure 1.8A. At the center of the cluster lies a pore that forms a small hole extending across the plasma membrane. When no ACh is bound to the receptor, the pore remains closed; when ACh binding occurs, the pore opens, allowing positively charged ions from the external fluid to flow into the muscle cell (described in detail in chapter 7). Thus, the ACh receptor forms an ACh-activated **ion channel** in the muscle membrane. The influx of positive charge through the channel makes the membrane potential of the muscle cell less negative (that is, the muscle cell depolarizes) in the presence of ACh, which triggers an action potential in the muscle cell.

As with the synthetic enzyme choline acetyl transferase and the degradative enzyme acetylcholinesterase, the presence of ACh receptors can be used as a marker for synapses that use ACh as a neurotransmitter. Figure 1.8B shows the localization of the receptors at the neuromuscular junction, as revealed by the binding of a toxin from snake venom that binds tightly to the ACh receptor site.

The neurons of the patellar reflex are part of larger neural systems

Let's return to the demonstration of the patellar reflex. Once again, cross one leg over the other and prepare to tap the patellar tendon to elicit the reflex. This time, however, command the muscles of your thigh to tense up and lock the knee joint in the flexed position. Now, when you tap the patellar tendon, no reflexive contraction of the quadriceps muscle and no reflexive extension of the lower leg occur. You have just demonstrated that the neurons of the patellar reflex are subject to control by other parts of the nervous system. This discovery comes as no surprise: voluntary override of spinal cord reflexes represents a mundane facet of our moment-by-moment existence. From the neurobiological point of view, specifying the neural circuitry involved in the voluntary control of motor function is a complex and incomplete task. In systems neurobiology, the goal is not to understand the functional role of a single neuron in the nervous system (although analysis of the behavior of individual neurons plays an important part in systems neurobiology), but rather to understand how groups of neurons are organized into larger neural circuits. The interactions among these neural circuits underlie the ability of the brain to carry out complex motor and sensory functions. We will now examine some of the circuits of which the neurons of the patellar reflex are components.

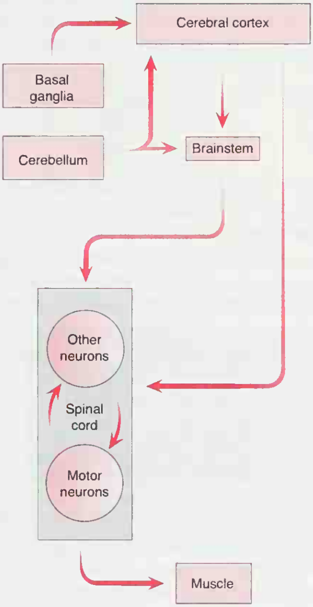
In Figure 1.2, we saw that the patellar reflex is the simplest kind of neuronal circuit, consisting of two types of neurons—the stretch-sensitive sensory neurons and the motor neurons—connected by a single synaptic connection. The motor neurons associated with a particular muscle (the quadriceps muscle in our example reflex) are part of many other spinal circuits as well. They represent the only means by which the nervous system can control the contraction of a muscle; therefore, any task that involves a particular muscle must be coordinated by neural circuits that converge onto the motor neurons supplying that muscle. In the case of the quadriceps muscle, the motor neurons will be acted upon by neural circuits involved in locomotion, by circuits involved in postural control and balance, and by any circuits that involve the knee joint.

Many of the neural circuits that influence the motor neurons consist of other kinds of neurons within the spinal cord itself, as shown schematically in Figure 1.9. These spinal neurons include various kinds of sensory neurons (in addition to the stretch-sensitive neurons already discussed) and numerous types of spinal cord **interneurons.** Interneurons are neurons that receive inputs only from other neurons and make outputs only to other neurons; in contrast, sensory neurons receive inputs from an external stimulus (for example, a muscle stretch) and motor neurons send outputs to non-neuronal targets (for example, muscle cells). In the central nervous system, most of the neural circuitry consists of interneurons.

Note also that the motor neurons send outputs not only to the muscle but also to the spinal neurons that make up the intraspinal circuits. Such feedback from a neuron to the cells from which it receives inputs is a common feature of neuronal circuits in the nervous system.

The neural circuits of the spinal cord coordinate various kinds of reflexive movements, in which a stimulus is closely coupled to a fixed motor output, without the requirement for conscious control or voluntary initiation of the movement. What about the voluntary control of movement, as when you prevented reflexive contraction of the quadriceps muscle by purposefully locking the knee joint before tapping the patellar tendon? Some of the brain circuitry involved in regulating spinal motor neuron function in this way is illustrated schematically in Figure 1.9. Clearly, the organizational scheme involved is rather complex and multiple parts of the brain work together in the controlling circuitry (more detailed information about this circuitry will be given in chapter 11). Commands for voluntary control of movement originate in the motor regions of the cerebral cortex, which sends signals directly to the spinal cord, as well as to brainstem motor nuclei. The brainstem neurons also send outputs to the spinal circuits. The movement commands from the cortex and brainstem are modulated by both the cerebellum and the basal ganglia (for simplicity, the inputs to the basal ganglia and cerebellum are excluded from Figure 1.9).

Figure 1.9
A block diagram of the motor control system, showing brain and spinal cord regions involved in formulating and executing motor commands. The diagram has been simplified by removing the sensory pathways providing inputs to many of the systems. In addition, the diagram does not include subdivisions of the cerebral cortex, basal ganglia, and brainstem motor regions.



The information needed to draw the diagram in Figure 1.9 comes from anatomical studies, which specify the connections between regions of the central nervous system and other regions, and from physiological studies, which specify how activity of one part affects the activities of other parts. Together, such information allows systems neurobiologists to deduce an overall picture of how parts interact to plan a movement, program its execution, and modify the movement on the basis of sensory feedback. Similar kinds of circuits could be drawn for the analysis of sensory information, as described in Part 4.

SUMMARY AND PREVIEW

In this overview, we have used a simple neural circuit—the patellar stretch reflex—to examine some examples of questions that neurobiologists ask about how the nervous system works. Even for a very simple neural circuit, we need many pieces of information about the cellular events in the circuit, the molecules that activate the cellular events, and the method in which the simple circuit fits in with larger neural systems. Although the approaches we have considered are quite diverse, they barely scratch the surface of the scientific questions that fall within the province of neurobiology.

For example, we have ignored the important question of how the nervous system reaches the adult form during the course of human development. How does the motor neuron become a motor neuron, rather than some other kind of neuron? How does the sensory neuron from the quadriceps muscle recognize and make synaptic connections with the motor neurons from the same muscle? How do the axons of the sensory and motor neurons find their way over long distances from the spinal cord to the target muscle?

From the molecular point of view, many questions lie beyond the scope of our current discussion. How does a gene that encodes a particular protein become turned on in one neuron but not another, or become active in neurons but not in glial cells? How do the proteins produced become targeted to the appropriate parts of the cell, especially when the parts of the cell may be more than one meter apart?

Most of the higher parts of the brain—particularly the cerebral cortex—are not directly concerned with either motor commands or sensory analysis per se, but rather with the integration of sensory and motor information. How do these integrating systems account for cognition—that is, the ability to plan and think? How does the nervous system modify itself and the way it controls the actions of the organism on the basis of past experience? How does the nervous system store and recall the information about those past experiences?

In this book, we will at least touch on many of these questions. We will not have answers to all of them—particularly those about complex neural systems—because many aspects of nervous system function remain unsolved mysteries. Instead, this book is intended to introduce ideas, concepts, and facts about neurons and the nervous system and to provide a framework for later learning. Students and instructors alike are invited to expand on the information contained here as their interests direct.

In Part 2, we begin by considering in detail the cellular signals discussed in this overview: the electrical and chemical signals involved in neuronal communication. To illustrate our discussion, we will continue to use the patellar reflex as a model system. In Part 3, we will turn our attention to the motor systems that regulate and control reflex action, which we have also briefly described in this chapter. Part 4 will discuss how sensory systems are organized to collect and analyze information about the environment that the organism faces. Finally, Part 5 will consider plasticity in the nervous system, both in terms of development and in terms of learning and memory.

2

Organization of Nervous Systems

The nervous system is a complex structure, with elaborate interconnections and communication networks among its various component parts. Because of this complexity, mastering the details of the neuroanatomy of advanced nervous systems, such as those possessed by mammals, is a difficult task. In this book, we have sought to make this task simpler by breaking the whole into its component parts, as defined by their functional roles. The anatomical organization of specific neural systems is then presented chapter-by-chapter, in conjunction with its physiological and functional description.

Although detailed neuroanatomy is considered later, it is helpful to first establish an overall framework of neural organization. In this chapter, we will look at some changes in neural organization that occurred over the course of evolution. The complex assembly that constitutes a mammalian brain can be more readily discerned if we examine simpler nervous systems and look for evolutionary trends in how nervous systems are organized. By studying simpler nervous systems, we can better appreciate the more complicated structures found in complex nervous systems. In a similar way, it is also useful to look at the development of the mammalian brain during embryogenesis, noting how the nervous system begins as a simple structure and becomes more complex as the organism matures. By examining the simpler structures that emerge during embryonic development, we can more easily see the interrelationships of the various parts of the adult nervous system, whose distinctions may not be so readily apparent in the adult form. In both viewpoints—evolutionary and developmental—we will utilize simpler forms to illustrate the organization that underlies more complex forms.

EVOLUTION OF NERVOUS SYSTEMS

Some of the themes underlying the organization of complex nervous systems can be best appreciated by examining less complex nervous systems and, in particular, evolutionary trends in the relationship between body form and style of living on the one hand and nervous system organization on the other. We will see that the basic plan of mammalian nervous systems (including our own) emerges as the outcome of four evolutionary trends in neural organization:

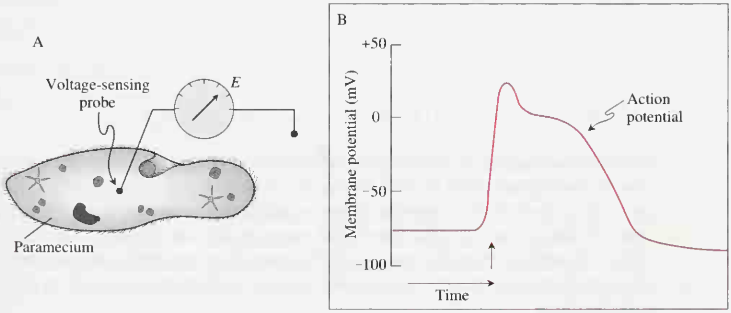
1. Evolution from radial symmetry to bilateral symmetry.
2. Evolution from general to specialized function of individual neurons.
3. Cephalization.
4. Hierarchical organization.

Before we explore some specific examples of these trends, we will spend some time considering the origin of neurons in multicellular organisms as cells specialized for communication of information.

Electrical signaling predates the emergence of neurons

Although it makes sense to talk about a "nervous system" (or any organ system for that matter) only in multicellular animals, even single-celled organisms possess some of the electrical mechanisms that we usually associate with neuronal function (see chapter 1 and the following section). For example, Figure 2.1 shows that the protozoan, *Paramecium,* can produce action potentials similar to those of nerve cells, except that the action potential results from an influx of calcium ions rather than sodium ions as in the typical nerve action potential (see chapter 5). Like nerve action potentials, the action potential in *Paramecium* also serves a coordinating function: it regulates the direction of ciliary beating and thus the cell's movement. Mutant paramecia that lack the ion channels underlying the calcium action potential cannot reverse the direction of ciliary beating and thus cannot swim backward when they encounter noxious environmental stimuli. Because the mutants can only swim forward, they are called "pawn"

Figure 2.1
The single-celled protozoan, *Paramecium,* can produce an action potential similar to a nerve action potential. The diagram on the left shows the recording system for measuring the electrical response of the outer membrane of the organism. The action potential elicited by an electrical stimulus (at the arrow) is shown on the right.



mutants, after the chess piece that can only move forward. Thus, some of the basic molecular machinery for electrical signaling—one of the hallmarks of nervous system function—vastly predates the origin of the first neuron. This suggests that neural signaling arose by the evolutionary modification of preexisting signaling mechanisms found in single-celled animals.

Pre-neuronal signaling systems also occur in multicellular animals that lack nervous systems. The cnidarian *Obelia,* for example, forms colonies of polyps sharing a common digestive system. Although there is no nervous system per se, electrical signals spread from one end of the colony to the other along the epithelial cells lining the interior of the digestive cavity of the organism. As in *Paramecium,* the signal takes the form of a calcium action potential.

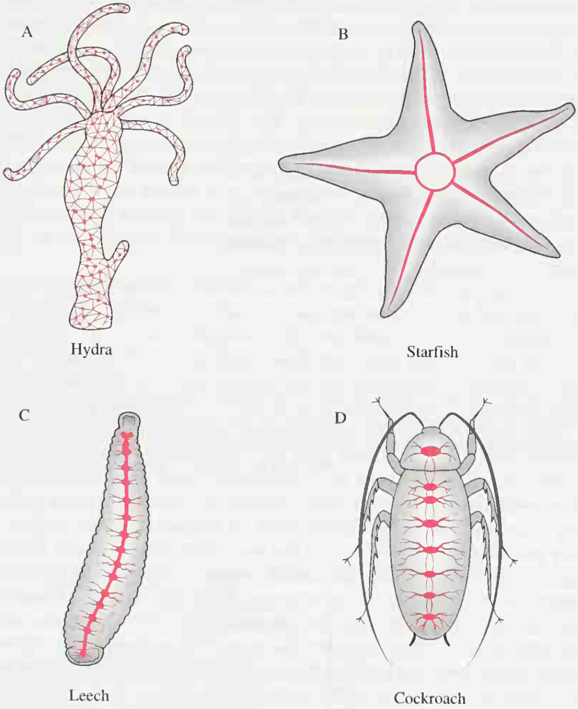
Other cnidarians, such as *Hydra,* have the first true nervous system. As shown in Figure 2.2A, this simple nervous system is organized into a **nerve net**, in which action potentials propagate from neuron to neuron equally well in all directions. In such a system, no particular neuron could be said to control the activity of another, and no part of the net demonstrates a specialization of function. The neurons of the nerve net can be regarded as providing a rapid conduction path for the spread of action potentials throughout the animal, as in the epithelial conduction system of *Obelia,* but with more rapid communication. True neurons, linked via nerve tracts containing the connecting axons, likely arose as a means to provide more rapid spread of signals in a more defined directional pattern than could be attained by electrical signals spreading nonspecifically throughout an epithelial sheet.

Free-swimming animals require well-coordinated movements to locomote effectively, and thus require nervous systems to coordinate their movements. Cnidarians such as jellyfish, for example, swim by rhythmic contractions of the bell and have well-developed nerve nets to ensure that the properly concerted contraction occurs. Interestingly, the free-swimming, reproductive medusae of *Obelia* have a nerve net, but the sessile adult animal does not. Thus, the evolutionary emergence of neurons may coincide with the origination of contractile tissues used for locomotion in animals.

Nerve nets like that of *Hydra* are commonly found in animals whose bodies show **radial symmetry**. In such animals, no particular body part is more likely than another to encounter food or predators. If the animal is mobile, any part might be likely to lead the way. This symmetry can also be readily seen in echinoderms, like the starfish shown in Figure 2.2B, in which a set of identical arms radiates from a central core. The starfish, however, shows the first indication of selective organization of the neurons into something other than a diffuse network; the innervation of each arm derives from a neural connective that radiates from a ring of nerve fibers surrounding a mouth located at the center of the animal. As nervous systems became more complex, this trend continued, evolving into more centralized organization of the cell bodies of neurons with nerve fibers radiating out from central clumps of neurons. Contrast this structure with the more diffuse organization of the nerve net, with the neurons spread throughout the network (see Fig. 2.2A).

Figure 2.2

Organization of nervous systems. (A) The most primitive nervous system consists of a diffuse nerve net, like that found in *Hydra*. (B) The nervous system of the starfish is organized in a central ring, with nerve fibers radiating out to supply each arm. (C) The leech has a body with bilateral, rather than radial, symmetry. Correspondingly, the nervous system is arranged longitudinally, reflecting the organization scheme seen in most animal nervous systems. The neuronal cells are centralized into ganglia along the animal's midline, with nerves radiating out to supply each body segment and large nerve trunks connecting the ganglia into a chain. (D) Insect nervous systems illustrate the evolutionary trend toward cephalization, with the ganglia at the head end of the animal growing in size and importance and fusing to form a true brain.



Bilateral symmetry and the emergence of centralized nervous systems

The trend toward centralized organization of the nervous system is most strongly apparent in animals whose bodies have **bilateral symmetry.** Compare the nervous system of a segmented annelid, the leech (Fig. 2.2C), with the more diffuse systems of *Hydra* and starfish. In the leech, the cell bodies of the neurons are gathered together in centrally located **ganglia,** one in each body segment. The nerves that innervate the muscles and skin of each segment radiate out from these central ganglia, and the ganglia of successive segments are connected via nerve fibers running longitudinally in a **central nerve trunk.** Specific sensory neurons in the ganglia carry sensory information gleaned from the environment, and motor neurons control the body muscles. In addition, integrative interneurons are interposed between sensory and motor neurons. Thus, the increased centralization of neural organization noted with the appearance of bilateral symmetry is also associated with less generalized and more specific information-processing functions for the individual neurons. This continuing theme—specialization of neuronal function—becomes more pronounced as organisms and their nervous systems become more complex.

Another trend that becomes evident with the advent of bilateral symmetry is the trend toward **cephalization,** which refers to the increasing size and importance of the ganglia at the head end of the animal. In most cases, animals with bilateral symmetry locomote in the direction parallel to the long axis of the body. As a result, the leading end of the animal usually comes into contact with food or other environmental stimuli first. The neurons in the ganglia at the animal's head end have increased importance, favoring the evolutionary development of larger and more complex cephalic ganglia. Among invertebrate animals, the insects have perhaps the most complex nervous systems and the most developed cephalic ganglia (Fig. 2.2D; some mollusks, such as the octopus, also possess complex cephalic ganglia).

As the segmental ganglia at the front end of the animal grew in size and complexity over evolutionary time, the individual ganglia fused into a single mass that could properly be termed a brain. Although a mammalian brain may not show obvious external signs of organization into clumps of nerve cells separated by interconnecting nerve fiber tracts (like the segmental organization of the leech), there are in fact many different clusters of neurons within the mammalian brain (called **nuclei** or **ganglia**) that receive inputs from and send outputs to other clusters. Thus, the more primitive organization into chains of interconnected ganglia can be discerned—albeit in much more intricate form—in the structure of more complex brains.

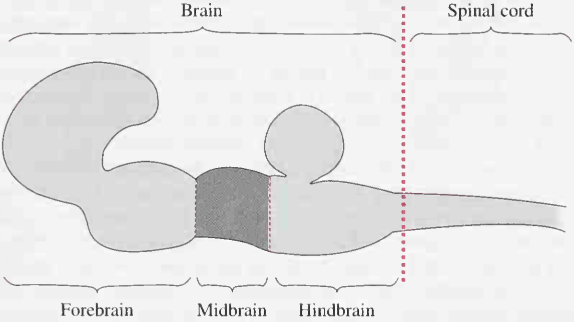
A corollary to the trend toward cephalization is the increased importance of cephalic regions in controlling the actions of the other parts of the nervous system. In more primitive nervous systems, each segmental ganglion coordinates the behavior of a particular body segment; although information is passed along the ventral nerve fibers from one ganglion to another, ganglia rarely control one another. With the appearance of cephalic ganglia and brains, however, **hierarchical organization** of the nervous system begins to emerge, with the ganglia in the head taking primary responsibility for the initiation of action and the overall integration of sensory and motor information into behaviors that make sense for the animal as a whole. The segmental ganglia in the rest of the body continue to control the local actions of individual body segments and integrate the local actions of the segment into the overall behavior of the animal. This trend is especially pronounced in vertebrate nervous systems, where it leads to the subdivision of the central nervous system into the brain (the overseer and initiator of behavior) and the spinal cord (coordinator of reflex actions and provider of circuitry for carrying out commands descending from the higher control centers of the brain).

Subdivisions of the vertebrate brain

In vertebrate animals, the brain is subdivided into three main regions (Fig. 2.3): the **hindbrain**, the **midbrain**, and the **forebrain**. In keeping with the general scheme of hierarchical organization, the hindbrain tends to pass information to and receive controlling signals from the midbrain, which is itself controlled by the forebrain. Of course, there are important exceptions to this hierarchical scheme, as we will see when we discuss the organizations of specific sensory and motor systems, but it is still useful to think about the organization of the brain in this hierarchical manner.

The hindbrain (also called the **rhombencephalon**) primarily coordinates relatively automatic body functions (such as respiration and cardiovascular function) and body movement. The midbrain (also called the **mesencephalon**) contains additional motor coordination centers; it also receives and processes sensory information, distributing it to the appropriate parts of the forebrain for further processing. Collectively, the midbrain and hindbrain are

Figure 2.3
The basic organizational scheme of the vertebrate central nervous system. The two major divisions are the spinal cord and brain; the brain is further subdivided into the forebrain, midbrain, and hindbrain.



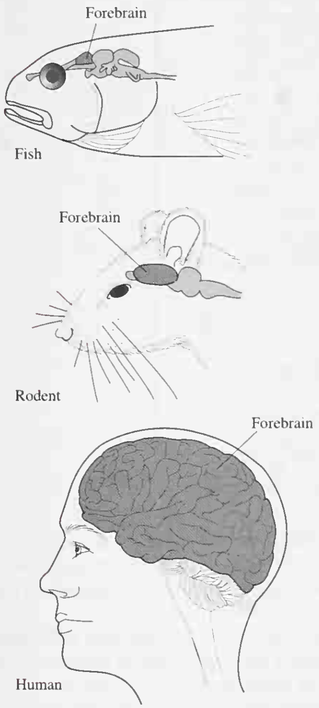


Figure 2.4
The relative proportions of the brain accounted for by the forebrain in a fish, a rodent, and a primate (human).

referred to as the **brainstem.** The forebrain (also called the **prosencephalon**) integrates sensory information of various kinds and formulates motor commands that are executed by other parts of the central nervous system.

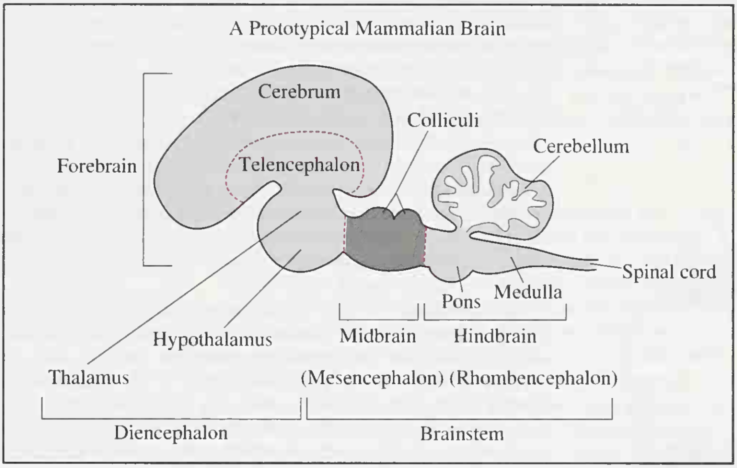
The trends toward increasing cephalization, increasing specialization of neural function, and hierarchical organization can be seen in the evolution of both invertebrate and vertebrate animals. In primitive vertebrates, such as fish, amphibians, and reptiles, the forebrain is a relatively minor part of the brain (Fig. 2.4). The functions carried out in this region in more complex brains are instead performed by midbrain regions in these animals. For example, in animals with primitive forebrains, visual information processing occurs in the optic tectum (part of the midbrain). In mammals, the corresponding parts of the midbrain are relegated to lower-level visual functions, such as the control of eye movements, while sophisticated visual processing is carried out in the forebrain.

In mammals, the increasing importance of the forebrain largely derives from the increased proportional size of a major subdivision of the forebrain, the **cerebrum** (see Fig. 2.4). The **cerebral cortex**, which is the outer layer of the cerebrum containing most of the neurons, balloons out to occupy a larger surface area, enveloping the more posterior midbrain and hindbrain structures. Thus, when we look at the exterior surface of a mammalian brain, our view is dominated by the cerebral cortex. In mammals more complex than rodents (see Fig. 2.4), the surface area of the cortex becomes so large that it must form infoldings, or **convolutions**, to fit within the space available for the brain inside the skull. The cerebral cortex is involved in complex processing of sensory information to form perceptions, in the planning and initiation of movements, and in associative learning. Therefore, increased surface area of the cortex—and thus increased numbers of cortical neurons—are correlated with increased complexity and flexibility of behavior.

The forebrain, midbrain, and hindbrain are each further subdivided into numerous parts that have their own specialized functions. Although we will discuss these subdivisions in detail in later chapters, it is worth mentioning some of them now to give an overall view of the structure of vertebrate brains.

The hindbrain has three principal subdivisions (Fig. 2.5): the **medulla oblongata**, the **cerebellum**, and the **pons**. The medulla oblongata sits at the junction between the brain and the spinal cord and contains neurons that help control many of the organism's visceral functions, such as breathing, swallowing, and digestion. The pons, which is located at the junction between the hindbrain and the midbrain, includes neurons that also regulate respiration. The cerebellum is a complex structure that receives a wide variety of sensory information as well as signals from motor control areas in the forebrain. Based on the sensory and motor information, it helps implement

Figure 2.5
The overall organizational structure of a prototypical mammalian brain, with a few of the prominent regions and subdivisions labeled.



coordination of the motor commands. Much of the space in the hindbrain is also occupied by the tracts of axons carrying ascending information from the spinal cord and descending control signals from higher centers to the spinal cord.

In the midbrain, two important subdivisions are the **inferior colliculus** and the **superior colliculus**, both of which form protrusions on the dorsal surface of the midbrain (see Fig. 2.5). The inferior colliculus is an important relay and processing station in the auditory system, while the superior colliculus is involved in processing visual information. Other parts of the midbrain make up a portion of the **reticular formation**, which controls the organism's level of arousal and contains neurons that play direct and indirect roles in a variety of motor and sensory systems.

The forebrain is divided into the **diencephalon** and the **telencephalon** (see Fig. 2.5). The diencephalon comprises the **thalamus** and **hypothalamus**, while the telencephalon consists of the cerebrum and the **basal ganglia**, which help control movement. The thalamus is a sensory relay station that distributes sensory information from the various sensory modalities to the appropriate parts of the cerebral cortex for more elaborate processing. The hypothalamus consists of a number of nuclei concerned with homeostasis (for example, hunger, thirst, and thermoregulation), with the control of sexual behavior, or with the regulation of emotion.

DEVELOPMENT OF THE NERVOUS SYSTEM

With its complex organization and large forebrain, the mammalian brain (see Fig. 2.5) represents the most fully developed example of the trends toward cephalization and hierarchical organization seen throughout the evolutionary development of progressively more complicated nervous systems. The divisions among the various regions of the brain may seem rather arbitrary, however, when we view the overall structure of the adult brain. Why does the brain contain three major divisions (forebrain, midbrain, and hindbrain)? How are the dividing lines between the three divisions set? Why is the forebrain subdivided into the telencephalon and diencephalon?

From an evolutionary perspective, we have seen that examining the brains of simpler organisms can provide clues about the major divisions of the brain. We will now consider the developmental sequence during embryogenesis of the mammalian brain to obtain a different perspective on the structural organization of the adult form. In the course of considering this developmental view, we will obtain some of the answers to our questions about the brain's seemingly arbitrary divisions.

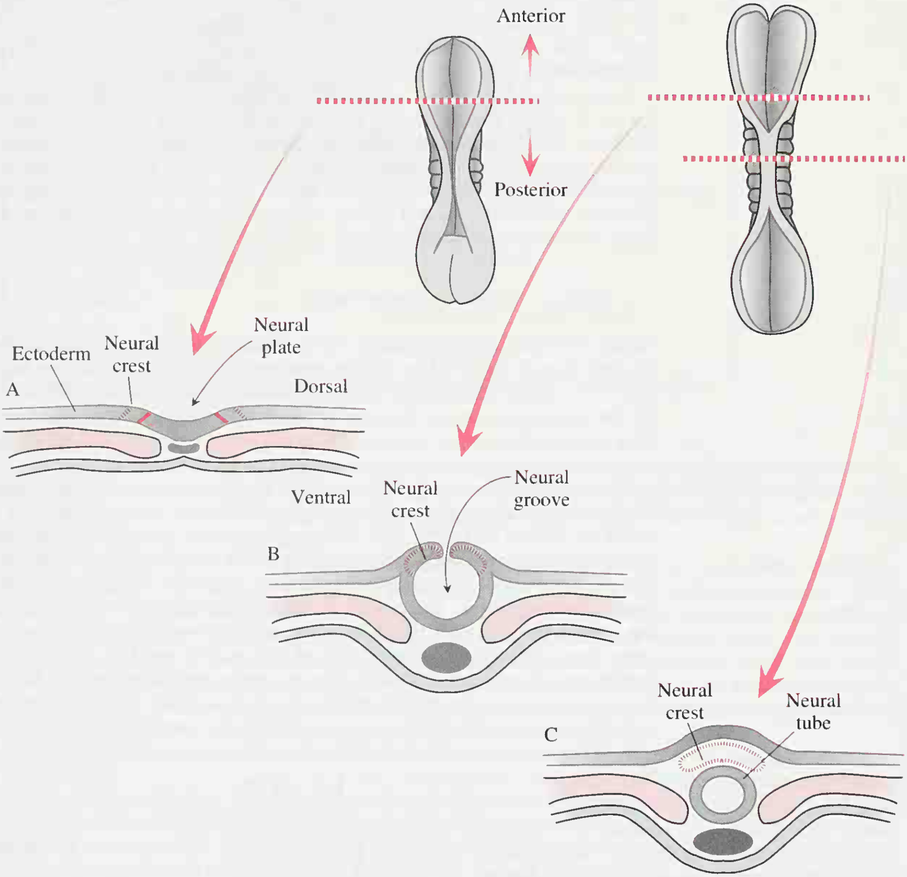
Early neural development

During embryonic development, the mammalian nervous system moves through several stages of increasing complexity, culminating in the adult form. The simpler forms found in the earlier stages can provide a perspective on the adult form, just as the simpler organization of nonmammalian nervous systems illuminated some of the underlying principles that led to the evolutionary development of more complex nervous systems.

The mammalian central nervous system begins as a specialized area along the dorsal midline of the ectoderm of the early-stage embryo; this area is called the **neural plate** (Fig. 2.6). Flanking the neural plate on each side are the cells of the **neural crest**, which give rise to the peripheral nervous system, including the dorsal root ganglia (discussed in chapter 1). As the cells of the neural plate proliferate, they create an indentation along the midline called the **neural groove**, with the cells of the neural crest forming the top (or crest—hence the name) of each side of the groove (see Fig. 2.6). As this indentation deepens, the lips of the groove come closer together and finally fuse. At this point, the neural groove becomes a sealed tubular structure, called the **neural tube**, which is separated from the overlying ectoderm. The cells of the neural crest lie between the neural tube and the ectoderm (see Fig. 2.6).

The cells lining the neural tube proliferate and differentiate into the neurons and glial cells that make up the brain and spinal cord. At the anterior end of the neural tube, which is destined to form the brain, cells proliferate more rapidly than at the posterior end, which will become the spinal cord. Thus, the anterior end begins to bulge out, forming three protrusions separated by constrictions, as shown in Figure 2.7. These protrusions, called **vesicles**, bear familiar names: the forebrain, the midbrain, and the hindbrain.

Figure 2.6
Early differentiation of the nervous system in a vertebrate embryo. (A) The nervous system begins as undifferentiated ectodermal cells along the dorsal midline, called the neural plate. At this stage, the cells that will form the neural crest (shown in pink) lie along each side of the neural plate. (B) At a later stage, the neural plate invaginates to form the neural groove, with the neural crest running along the lips of the groove. (C) Later, the neural groove pinches off to form the neural tube, as the two opposing parts of the neural crest fuse.

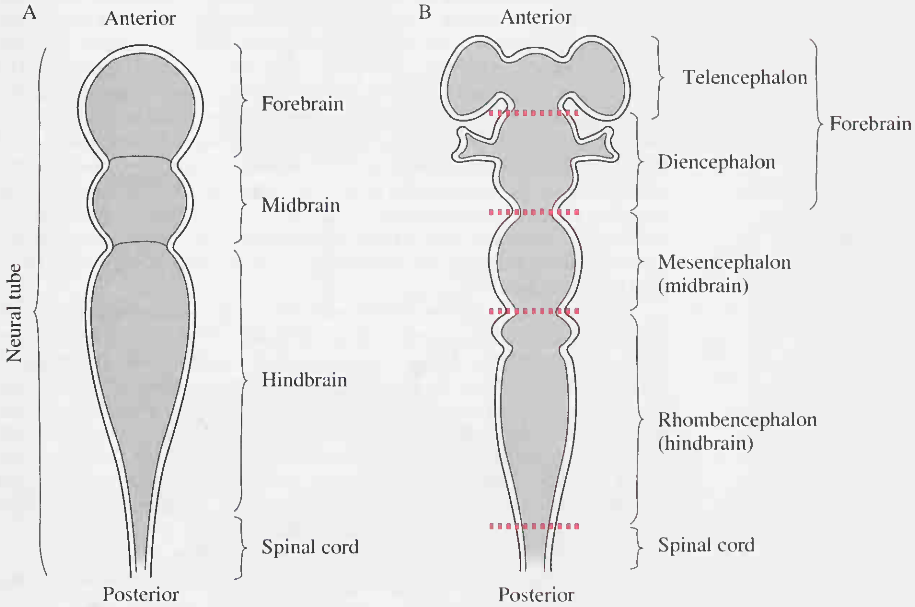


The part of the neural tube posterior to the three vesicles is the spinal cord. It should now be clear why the adult brain is divided into three major parts: three is the number of proto-brain protrusions that form early in the development of the central nervous system.

As development proceeds, the lateral portions of the forebrain vesicle begin to balloon out into structures that will become the two hemispheres of the cerebrum (see Fig. 2.7). Thus, the subdivision of the forebrain into the telencephalon and diencephalon also has an origin in the embryonic development of this part of the brain: the large protrusions form the telencephalon, while the part left behind forms the diencephalon. A similar subdivision of the hindbrain into its component parts—including the pons, cerebellum, and medulla—begins at these embryonic stages as well (see Fig. 2.7). The assignment of a particular structure in the adult brain to the forebrain, midbrain, or hindbrain is, therefore, determined by which of the primordial brain vesicles gave rise to the structure.

Figure 2.7

Development of the brain at the anterior end of the neural tube. (A) At a primitive stage of development, the anterior neural tube expands into three vesicles: the hindbrain, midbrain, and forebrain. (B) As development proceeds, the hindbrain and forebrain vesicles subdivide further.



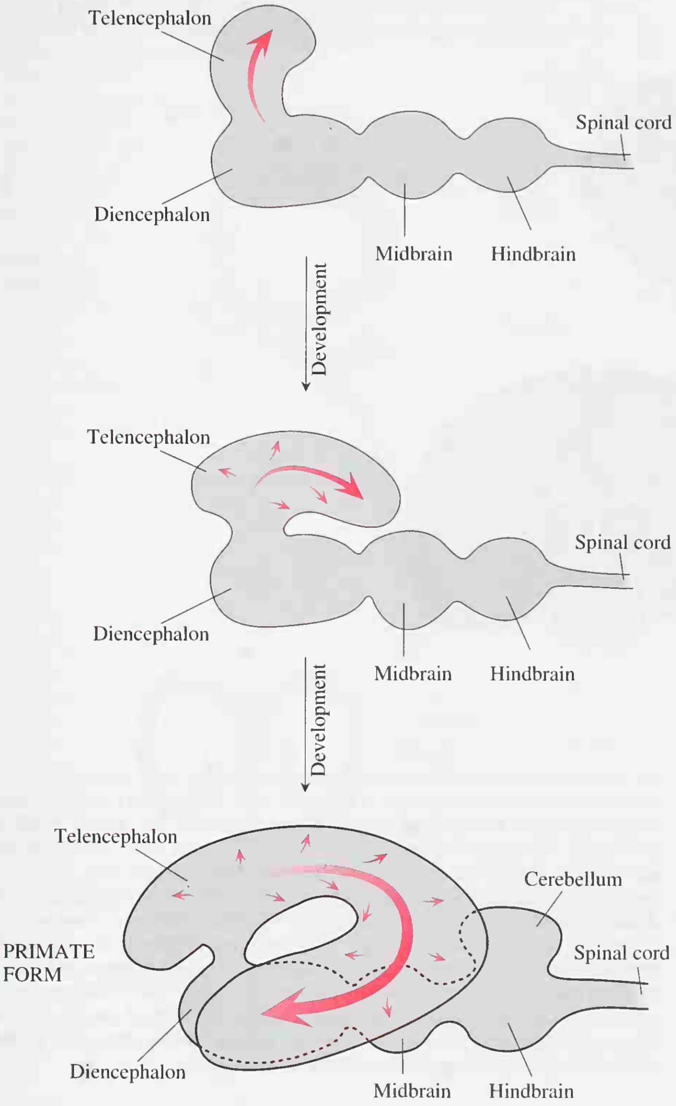
As the telencephalon grows, it folds back on itself, overlapping and enveloping the midbrain and parts of the hindbrain, as illustrated in Figure 2.8. In animals with large cortical regions, such as primates, the growing telencephalon turns back on itself once again, forming a shape somewhat like a ram's horn (see Fig. 2.8). Because of the complex folding and overlapping, the hierarchical structure of the adult brain may be hard to appreciate without considering the developmental sequence. For example, a cross section of the human brain taken approximately through the middle of the brain (Fig. 2.9) would contain some structures from the telencephalon, some from the diencephalon, and some from the midbrain; the divisions among the parts might appear unclear and arbitrary. If we remember the embryonic sequence and the simpler primordial structures, however, then the complex adult shape can be regarded as an elaboration of this scheme.

The vertebrate nervous system is a fluid-filled tube

Although the hierarchical structure and the gross divisions and subdivisions of the adult mammalian brain may not be readily apparent from the brain's outward appearance or cross-sectional views, one aspect of its overall morphology does help clarify the linear connection among the various brain regions and their origins as elaborations of a simple fluid-filled tube. That aspect is the hollow core contained within the tube. Earlier, we noted that the brain and spinal cord form from the neural tube, a hollow structure formed by pinching off the neural groove from the embryonic ectoderm. The hollow core of the tube persists into adulthood, where it consists of the **spinal canal** in the spinal cord and the **cerebral ventricles** in the brain. The tube is filled with **cerebrospinal fluid** (CSF). The ventricles and spinal canal form a continuous fluid compartment that extends from the tail-end of the spinal cord to the hemispheres of the cerebral cortex. By tracing along this corridor, we can follow the linear path from spinal cord to hindbrain to midbrain to forebrain, even though the route includes numerous bends and turns introduced during the differentiation of the simple embryonic structure into the adult form.

The shape taken by the ventricles in the adult human brain (Fig. 2.10) reflects the embryonic growth and proliferation of the various parts of the brain. As it enters the brain, the spinal canal expands to form the fourth ventricle at the core of the hindbrain. Through the midbrain, the ventricle narrows again to form a structure called the **cerebral aqueduct**. In the diencephalon, the aqueduct opens dorsally and ventrally to form the tall, thin **third ventricle**. As the telencephalon balloons out from the diencephalon during development, the ventricles expand laterally to form the two **lateral ventricles**, one in each hemisphere of the cerebrum. The expansion of the telencephalon continues posteriorly, ventrally, and then anteriorly; the lateral ventricles follow suit. Thus, the adult lateral ventricles clearly show the ram's horn shape resulting from this direction of expansion during development (see Fig. 2.10).

Figure 2.8
Development of the telencephalon. As the cerebral cortex expands, it extends in the posterior direction to overlie the midbrain and hindbrain. In animals with larger cortices, the growing telencephalon curls around into a shape similar to that of a ram's horn and virtually completely surrounds the midbrain structures and the diencephalon.



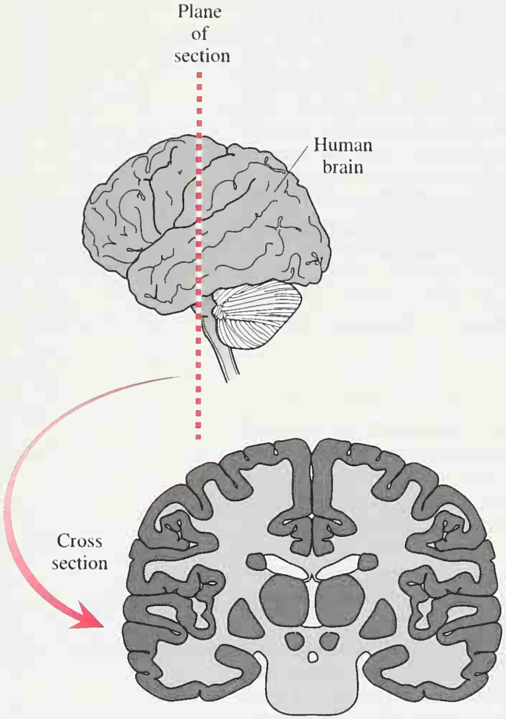


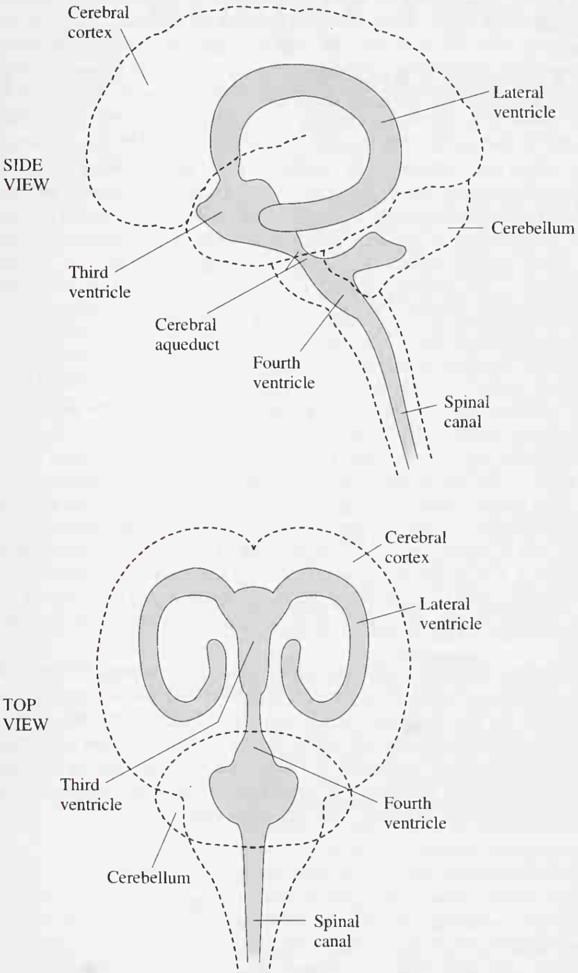
Figure 2.9
A human brain is cut in half perpendicular to the midline to reveal the brain structures in cross section. The slice cuts through forebrain and midbrain structures.

Functional neuroanatomy

We have now considered the overall structure of vertebrate—especially mammalian—nervous systems, both as an example of evolutionary trends toward larger and more hierarchical central nervous systems and as the result of embryonic development from simpler structures. We have discussed the subdivision of the brain into gross structural parts, which will provide a framework of nomenclature and a conceptual reference point for our more detailed discussions of brain organization found in subsequent chapters.

In this book, we take the view that the most important aspect of the nervous system is how neurons are organized into neural systems, as defined by their function for the animal. Forebrain, midbrain, and hindbrain structures might all contribute to the same functionally defined neural system. The anatomical organization of a neural system will be discussed in the context of the physiological description of that system.

Figure 2.10
The organization of ventricles in the human brain. The developmental expansion of the telencephalon is reflected in the shape of the lateral ventricles. In addition, the continuity of the ventricles from the spinal canal to the tips of the lateral ventricles demonstrates the brain's underlying form—that of a contorted tube.



SUMMARY

The overall structure of the mammalian central nervous system can be better appreciated by examining the development of the nervous system, in terms of both evolutionary origin and embryonic development. Neurons probably arose during evolution as a specialization that provided rapid and reliable control of motor structures and rapid distribution of sensory information. Electrical signaling, which is found in single-celled animals, predates the development of nervous systems. The simplest nervous systems are nerve nets like those found in *Hydra,* in which electrical signals can propagate from neuron to neuron in any direction throughout the network. The development of animals with bilateral symmetry (for example, worms), rather than radial symmetry (exemplified by starfish) was accompanied by the clustering of neurons along the midline of the animal to form ganglia along a centralized nerve cord, instead of a diffuse nerve net. As nervous systems became more complex, the ganglia at the front end (the head) of the animal became larger and more important in the control of the rest of the nervous system, a process called cephalization. The dominance of the head ganglia in controlling the rest of the nervous system represents an example of the evolutionary trend toward hierarchical organization of the nervous system.

The organization of the vertebrate nervous system can be more easily comprehended by examining the relatively simple structure of the nervous system early in embryonic development. The nervous system develops from a fluid-filled tube, called the neural tube, which is formed from the neural plate of the early embryo. As development proceeds, the anterior part of the neural tube bulges out to form three protrusions, or vesicles, that give rise to the three parts of the vertebrate brain: the hindbrain, the midbrain, and the forebrain. The lateral portions of the forebrain vesicle balloon out to form the two hemispheres of the cerebrum, forming the cerebral cortex, which then spreads out to cover most of the midbrain and hindbrain in mammalian nervous systems. The developmental history of a complex mammalian brain can also be appreciated by examining the three-dimensional structure of the fluid-filled center of the nervous system, the cerebral ventricles and the spinal canal.

The forebrain, midbrain, and hindbrain can each be subdivided into numerous subregions, based on anatomical connections and the subregions' functional roles. In the hindbrain, three major subdivisions are the medulla oblongata, the cerebellum, and the pons. In the midbrain, three important subregions are the superior colliculus, the inferior colliculus, and the reticular formation. The two main subdivisions of the forebrain are the telencephalon, which includes the cerebral cortex, and the diencephalon.

PART II

Cellular Aspects of Neurobiology

In this section of the book, we will examine the fundamental properties of communication in the nervous system. The nervous system is an electrical communication system, and we cannot understand its functioning without a firm understanding of how electrical signals are generated and transmitted in nerve cells. To illustrate the electrical behavior of neurons, we will return to the patellar reflex, which we introduced in chapter 1, because the electrical signals that underlie information transmission in the nervous system are represented in a simple way in this reflex.

As we saw in chapter 1, information must be transmitted over a long distance in the patellar reflex—along the axons of the sensory and motor neurons in the nerve connecting the spinal cord and the quadriceps muscle. The electrical signal that mediates the transmission of this information is the action potential. Our first step in studying the cellular mechanisms that produce the action potential will be to elucidate the physical and chemical principles that govern the generation of the electrical membrane potential in cells. This conceptual foundation will permit us to understand the electrical properties of neurons. Our next step will be to apply the principles that govern the membrane potential to understanding the mechanisms that allow neurons to actively modulate the membrane potential, thereby producing the action potential. Finally, we will turn our attention to communication among neurons, and examine mechanisms of synaptic transmission.

Chapters 3 and 4 will focus on osmotic and electrical equilibrium as well as non-equilibrium steady-state membrane potential of cells. We will develop a series of model systems that illustrate the important principles underlying the electrical membrane potential of cells. Each model system is tailored to illustrate a particular principle. As we proceed through these chapters, the models will become progressively more complex and more realistic. In this way, even students who lack a quantitative background in physics and chemistry should be able to reach an understanding of the principles that govern the electrical behavior of cells. In chapters 5 and 6, we will apply these principles in examining the membrane mechanisms underlying the action potential. Chapters 7 and 8 will consider synaptic transmission, first from motor neurons to muscle cells at the neuromuscular junction, and then from neuron to neuron in the spinal cord.

In Part 3, which begins with chapter 9, we will move on from this cellular viewpoint to see how the patellar reflex meshes with the overall scheme of motor control systems in both the spinal cord and the brain.

3

Osmotic Balance and the Maintenance of Cell Volume

In chapters 4 and 5, we will examine how electrical voltage gradients arise across the membranes of cells. In the nervous system, changes in the membrane voltage gradient—that is, the membrane potential—are central to the generation and processing of signals. Before we can identify how those changes occur, however, we must first understand the basic physical and chemical principles that govern the generation of electrical fields in cells. These principles apply to all cells, not just to neurons. We will develop these concepts systematically through a sequence of model systems and schematic distillations of experimental results. In this chapter, we will set the stage by noting important differences in the composition of intracellular and extracellular fluids and by describing the mechanisms through which osmotic balance is maintained. In chapter 4, we will turn our attention to the principles of ionic equilibrium and the membrane mechanisms for sustaining a nonequilibrium ionic steady state.

COMPOSITION OF INTRACELLULAR AND EXTRACELLULAR FLUIDS

When we think of biological molecules, we normally envision the special molecules that are unique to living organisms, such as proteins and nucleic acids: enzymes, DNA, RNA, and so on. These are the substances that allow life to occur and that give living things their special characteristics. Yet, if we were to dissociate a human body into its component molecules and then sort those molecules by type, we would find that these special molecules are only a small minority. Of all the molecules in a human body, only about 0.25% are special biological molecules. Most are far more ordinary. In fact, the most common molecule in the body is water. Excluding nonessential body fat, water makes up approximately 75% of the weight of a human body. Because water is a relatively light molecule, especially when compared with massive protein molecules, this percentage translates into a staggering number of molecules—99% of all molecules in the body. The remaining 0.75% of molecules consists of other simple inorganic substances—mostly sodium, potassium, and chloride ions. In this section of the book, we will be concerned largely with the mundane majority of molecules, the 99.75% made up of water and inorganic ions.

Why should we study these mundane molecules? Although many enzymatic reactions involving the more glamorous organic molecules require the participation of inorganic cofactors, and although most biochemical reactions within cells occur among substances that are dissolved in water, the reality is that most inorganic molecules in the body never participate in a biochemical reaction. Nevertheless, cells could not exist and life as we know it would be impossible if cells did not possess mechanisms to control the distribution of water and ions across their membranes. In this chapter, we will investigate why this is true and will identify the physical principles that underlie the ability of cells to maintain their integrity in a hostile physicochemical environment.

Intracellular and extracellular fluids

The water in the body can be divided into two compartments: intracellular and extracellular fluid. Approximately 55% of the water is inside cells, and the remainder is outside. The extracellular fluid (ECF) can itself be subdivided into plasma, lymphatic fluid, and interstitial fluid. For now, however, we will lump all ECF together into a single compartment. Similarly, cells contain various subcompartments, but it will suffice for now to treat them as uniform bags of fluid. The wall that separates the intracellular and extracellular fluid compartments is the outer cell membrane, also called the **plasma membrane** of the cell.

Although organic and inorganic substances are dissolved in both intracellular and extracellular water, the compositions of the two fluid compartments differ. Table 3.1 gives simplified compositions of ECF and intracellular fluid (ICF) for a typical mammalian cell, listing only those substances that are important in governing the basic osmotic and electrical properties of cells. A variety of other inorganic and organic solutes are found in both ECF and ICF, and many of them have important physiological roles in other contexts. For our present purposes, however, they can be safely ignored.

The principal cation (positively charged ion) outside the cell is sodium, although a small amount of potassium is present as well (the potassium will become an important consideration when we discuss the origin of the membrane potential of cells). Inside cells, the situation is reversed. In ICF, the principal cation is potassium, with only a small amount of sodium. Negatively charged chloride ions, which are present at high concentration in ECF, are relatively scarce in ICF. The major anion (negatively charged ion) inside cells is actually a class of molecules that bear a net negative charge. These intracellular anions (abbreviated as A^-) include protein molecules, acidic amino acids such as aspartate and glutamate, and inorganic ions such as sulfate and phosphate. For the purposes of this book, the anions of this class outside cells can be ignored; we will assume that the only extracellular anion is chloride.

Table 3.1 Simplified compositions of intracellular and extracellular fluids for a typical mammalian cell.

	Internal Concentration (mM)	External Concentration (mM)	Can It Cross Plasma Membrane?
K^+	125	5	Y
Na^+	12	120	N*
Cl^-	5	125	Y
A^-	108	0	N
H_2O	55,000	55,000	Y

Membrane Potential = -60 to -100 mV

*As we will see in chapter 4, this "no" is not as simple as it first appears.

We must also take into account the concentration of water on the two sides of the membrane (see Table 3.1). It may seem odd to speak of the "concentration" of the solvent in ECF and ICF. As our discussion of the maintenance of cell volume will show, however, the concentration of water inside and outside the cell must be the same. If it differs, water will move across the membrane and cell volume will change.

It will also be important to consider each substance's ability to cross the plasma membrane—that is, the membrane's permeability to that substance. The plasma membrane is permeable to water, potassium, and chloride, but is effectively impermeable to sodium (sodium permeability will be discussed in depth later). Of course, if the membrane is to do its job properly, it must keep the organic anions inside the cell; otherwise all of a cell's essential biochemical machinery would simply diffuse away into the ECF. Thus, the membrane is impermeable to A^-.

To measure the electrical voltage difference between the inside and outside of an animal cell, an ultrafine probe, called an intracellular microelectrode, can be inserted inside the cell. The inside of the cell is more negative than the outside. The difference, which usually lies in the range of 60 to 100 millivolts (mV), is known as the **membrane potential** of the cell. By convention, the potential outside the cell is called zero; therefore, the typical value of the membrane potential (abbreviated E_m) is -60 to -100 mV (see Table 3.1). Chapter 4 will focus on the origin of this electrical membrane potential. In both chapters 4 and 5, we will discuss how it influences the movement of charged particles across the cell membrane and how the electrical energy stored in the membrane potential can be tapped to generate signals that can be passed from one cell to another in the nervous system.

The structure of the plasma membrane

Before considering the mechanisms that allow cells to maintain the differences in ECF and ICF shown in Table 3.1, let us examine the structure of the plasma membrane. The control mechanisms responsible for the differences between ICF and ECF reside within that barrier between the intracellular and extracellular compartments.

It has long been known that, if a cell is damaged by being poked or prodded with a glass probe, its contents will leak out. In addition, some dyes will not enter cells when dissolved in the extracellular fluid; the same dyes will not leak out when injected inside cells. These observations, which were first made in the nineteenth century, led to the idea that a selectively permeable barrier—the plasma membrane—separates the intracellular and extracellular fluids.

The first systematic observations of the kinds of molecules that could enter cells and the kinds that were excluded were made by Overton in the early twentieth century. He found that, in general, substances that are highly soluble in lipids enter cells more easily than substances that are less soluble in lipids. Lipids are molecules that are not soluble in water or other polar solvents, but are soluble in oil or other nonpolar solvents. Thus, Overton suggested that the plasma membrane of a cell consists of lipids and that substances can cross the membrane if they prove capable of dissolving in that lipid barrier.

There are some exceptions to the general lipid solubility rule. Electrically charged substances, such as potassium and chloride ions, are almost totally insoluble in lipids, yet they manage to cross the plasma membrane. Other substances, such as urea, enter cells more easily than might be expected from their lipid solubility alone. To account for these exceptions, Overton suggested that the lipid membrane is peppered with tiny holes or pores that allow highly water-soluble (hydrophilic) substances, such as ions, to cross the barrier. Only hydrophilic substances that are small enough to fit through these small aqueous pores can pass through. Larger molecules, such as proteins and amino acids, are unable to fit through the pores and thus cannot cross the membrane without the help of special transport mechanisms.

The molecules of the lipid skin surrounding cells appear to be arranged in a layer that is only two molecules thick. Evidence for this arrangement was obtained from experiments in which the lipids were chemically extracted from plasma membranes and spread out on a trough of water in such a way that they formed a film only one molecule thick. When the area of this monolayer "oil slick" was measured, it was found to be about twice the total surface area of the intact cells from which the lipids were obtained. This suggests that the membrane of the intact cells was two molecules thick. Hence, it is called a **lipid bilayer membrane.**

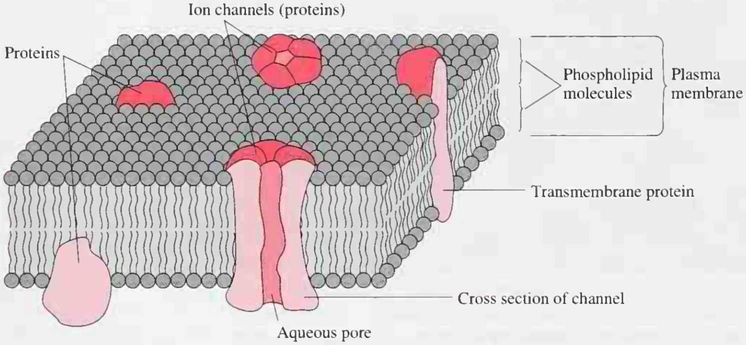
The bilayer arrangement of the cell membrane makes chemical sense when we consider the characteristics of the kinds of lipid molecules found in the plasma membrane. The cell lipids are largely phospholipids—that is, molecules possessing both a hydrophilic polar region and a hydrophobic nonpolar region. When surrounded by water, these lipid molecules tend to aggregate, with the hydrophilic regions oriented toward the surrounding water and the hydrophobic regions pointed toward one another. When spread out in a sheet with water on each side of the sheet, the phospholipids can maintain their preferred state by forming a bimolecular sandwich, with the hydrophilic parts on the outside, pointed toward the water, and the hydrophobic parts in the middle, pointed toward one another (Fig. 3.1).

Cell membranes contain not only lipid molecules but also protein molecules (see Fig. 3.1). Some proteins are attached to the inner or outer surface of the cell membrane, while others penetrate through the membrane and form a bridge from one side to the other. Some of these transmembrane proteins form the aqueous pores, or channels, that allow ions and other small hydrophilic molecules to cross the membrane. By weight, only roughly one-third of the cell membrane material is lipid; most of the remainder is protein. Although the lipids form the backbone of the membrane, proteins represent an important part of the picture. As we will see later, proteins help control the movement of substances, particularly ions, across the cell membrane.

The importance of membrane proteins for life can be seen by examining how much of the entire genome of a simple organism consists of genes encoding membrane proteins. One of the smallest genomes possessed by any free-living organism is that of *Mycoplasma genitalium*, a microbe whose genome can be regarded as nearly the minimum required for an independent, cellular life form. The DNA of *M. genitalium* has been completely sequenced, revealing a total of 482 individual genes. Of this total, 140 genes (approximately 30%) code for membrane proteins. Thus, *M. genitalium* expends a large fraction of its total available DNA for the membrane proteins that reside at the interface between the microbe and its external

Figure 3.1

A schematic diagram of a section of the plasma membrane. The backbone of the membrane is a sheet of lipid molecules two molecules thick. Inserted into this sheet are various types of protein molecules. Some protein molecules extend across the sheet, from the inner face to the outer face. These transmembrane proteins sometimes form small-diameter aqueous pores or channels through which small hydrophilic molecules, such as ions, can cross the membrane. The diagram shows two such channels; one is cut in cross section to reveal the interior of the pore.

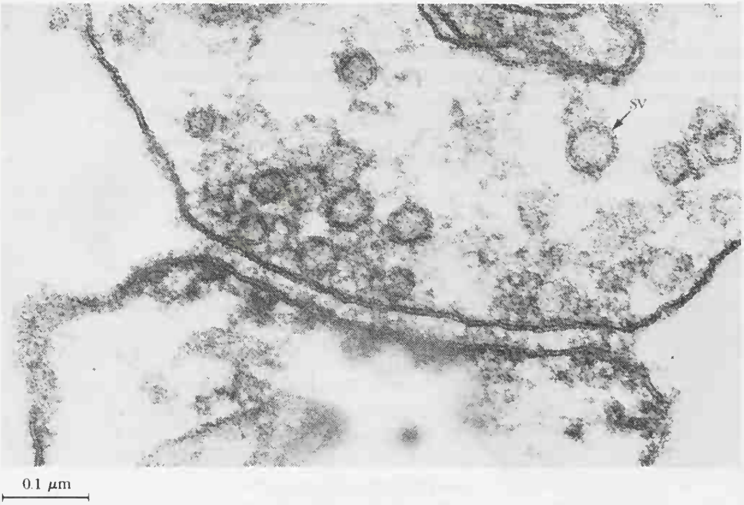


environment. This relationship points out the central role that these proteins play in the maintenance of cellular life.

Anatomical evidence also supports the bilayer cell model. The cell membrane is much too thin to be seen with the light microscope, and almost too thin to be seen with the electron microscope. With an electron microscope, one can see a three-layered (trilaminar) profile like a railroad track at the cell's outer boundary, with a light region separating two darker bands. The dark bands represent the polar heads of the membrane phospholipids and protein molecules on the inner and outer surfaces of the membrane. The lighter region between the two dark bands represents the nonpolar tails of the lipid molecules. The total thickness of the sandwich is approximately 7.5 nm.

Figure 3.2 provides an example of an electron micrograph showing the plasma membranes of two nerve cells (neurons) in the brain that lie in close contact. The lighter-colored "fuzz" surrounding the trilaminar profiles of the

Figure 3.2
A high-power electron micrograph of the plasma membranes of two neighboring cells. Note the two dark bands separated by a light region at the outer surface of each cell. The two cells are nerve cells from the brain, and the point of close contact between them is a synapse, the point of information transfer in the nervous system. Note also the membrane-bound intracellular structures (labeled *SV*), called synaptic vesicles, inside one of the cells. The vesicle membranes demonstrate the same trilaminar profile seen in the plasma membranes. (Synaptic vesicles and synapses are discussed in more detail in chapters 7 and 8.)



Courtesy of A. L. deBlas of the University of Missouri, Kansas City.

membranes consists in part of portions of membrane-associated protein molecules extending out into the intracellular and extracellular spaces. The region of close contact is the specialized junction, called the synapse, where electrical activity is relayed from one nerve cell to another.

By using a special form of microscopy called freeze-fracture electron microscopy, we can visualize more clearly the protein molecules that are embedded in the plasma membrane. A schematic representation of this technique is shown in Figure 3.3. A small sample of the tissue is frozen in liquid nitrogen, and then a thin sliver is shaved off with a sharp knife. Because the tissue is frozen, however, the sliver is actually broken off (rather than sliced) from the sample. In some cases (see Fig. 3.3), the line of fracture runs between the two lipid layers of the membrane bilayer, leaving holes where protein molecules are ripped out of the lipid monolayer and protrusions where membrane proteins are ripped out of the opposing monolayer with the shaved sliver. Figure 3.4 shows a freeze-fracture sample viewed through the electron microscope. The membrane proteins appear as small bumps in the otherwise smooth surface of the plasma membrane, like grains of sand sprinkled on a freshly painted surface. In the discussion of the transmission of signals from one nerve cell to another in chapter 5, we will see other examples of freeze-fracture electron micrographs and see how they can provide important evidence about the physiology of cells.

SUMMARY OF IONIC COMPOSITION OF INTRACELLULAR AND EXTRACELLULAR FLUIDS

The most common molecules in the body are water and simple inorganic molecules—mainly sodium, potassium, and chloride ions. The water in the body can be divided into two compartments: the intracellular and extracellular fluids. The compartments are separated by the cell's plasma membrane, which is a phospholipid bilayer into which protein molecules are inserted. The ECF contains high concentrations of sodium and chloride, but a low concentration of potassium; in contrast, the ICF is low in sodium and chloride, but high in potassium. This difference is maintained and regulated by control mechanisms residing within the plasma membrane, which acts as a selectively permeable barrier, permitting some substances to pass through but excluding others.

MAINTENANCE OF CELL VOLUME

At an early stage of evolution, before the development of cells, life might well have consisted of a loose confederation of enzyme systems and self-replicating molecules. A major problem faced by such acellular systems must have been keeping their constituent parts from simply diffusing away into the

Figure 3.3

A schematic illustration of the freeze-fracture procedure for electron microscopy. When a fracture line runs between the two lipid layers of the plasma membrane, some membrane proteins stay with one monolayer, others with the other layer. When examined with the electron microscope, the remaining proteins appear as protruding bumps in the fractured surface.

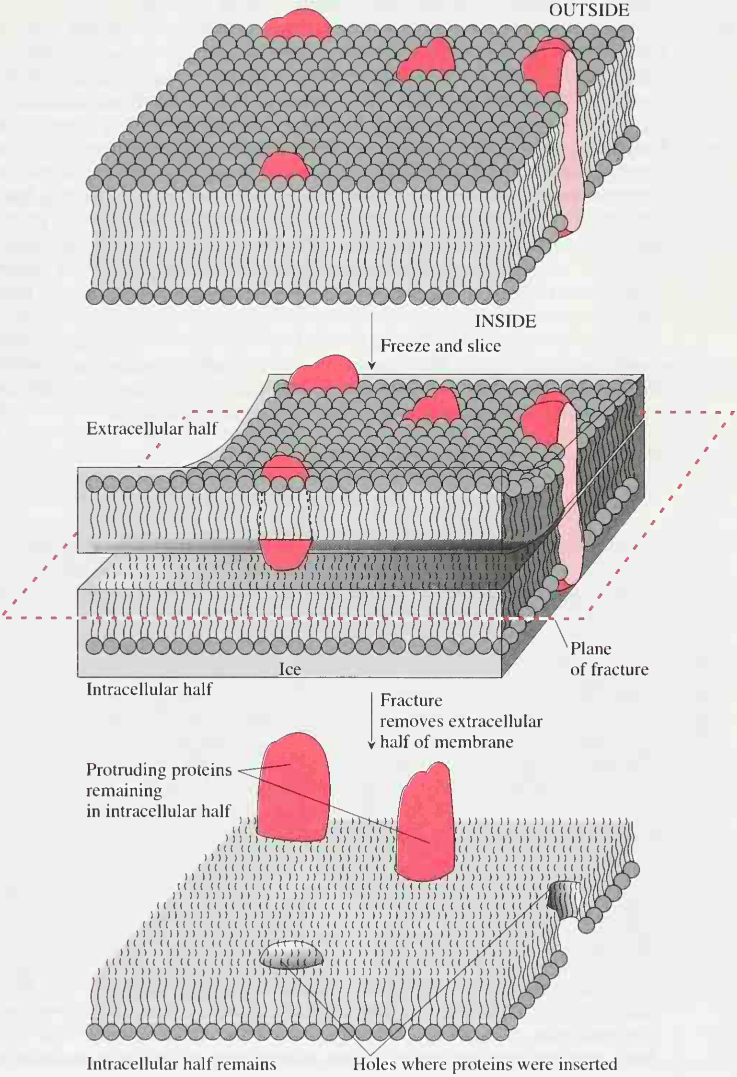
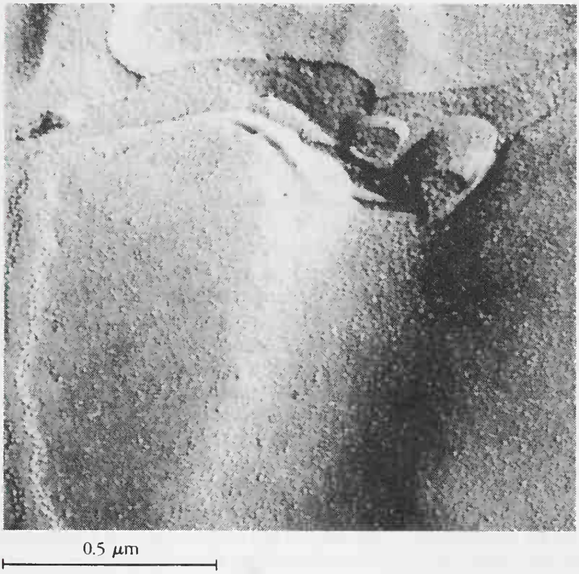

OUTSIDE
INSIDE
Freeze and slice
Extracellular half
Ice
Intracellular half
Plane of fracture
Fracture removes extracellular half of membrane
Protruding proteins remaining in intracellular half
Intracellular half remains
Holes where proteins were inserted

Figure 3.4
An example of a fractured membrane surface containing protein molecules, viewed through the electron microscope. The membrane surface here is that of the presynaptic nerve terminal at the nerve–muscle junction (discussed in detail in chapter 7). The protein molecules are the small bumps scattered on the planar surface of the membrane.



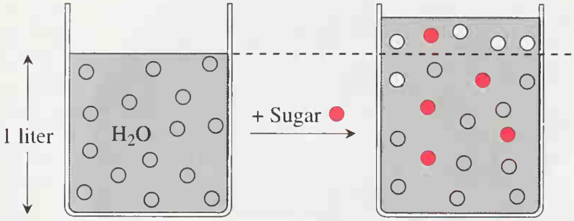
Reproduced with permission from Ko C-P. Regeneration of the active zone at the frog neuromuscular junction. J Cell Biol 1984;98:1685–1695 by copyright permission of the Rockefeller University Press.

surrounding murk. The solution to this problem involved the development of a cell membrane that was impermeable to these organic molecules; this evolutionary step represented the beginning of cellular life. The cell membrane, while solving one problem, brought with it a new problem: the need to achieve osmotic balance. To see how this problem arises, it will be useful to review solutions, osmolarity, and osmosis. We will then analyze the cellular mechanisms used to deal with problems of osmotic balance.

Molarity, molality, and diffusion of water

Imagine a situation in which we take one liter of pure water and dissolve some sugar in it (Fig. 3.5). The dissolved sugar molecules take up some space that was formerly occupied by water molecules, causing the volume of the

Figure 3.5
When sugar molecules (red circles) are dissolved in a liter of water, the resulting solution occupies a volume greater than one liter because the sugar molecules take up space formerly occupied by water molecules (white circles). As a result, the concentration of water (number of molecules of water per unit volume) is lower in the sugar–water solution.



solution to increase. Recall that the concentration of a substance is defined as the number of molecules of that substance per unit volume of solution. In Figure 3.5, the concentration of water in the sugar–water solution is lower than it was in the pure water before the addition of the sugar. This is because the total volume increased after the sugar was dissolved, but the total number of water molecules remained the same before and after.

To compare the concentrations of water in solutions containing different concentrations of dissolved substances, we will use the concept of **osmolarity.** A solution containing 1 mole of dissolved particles (that is, solute) per liter of solution (a 1 molar, or 1 *M*, solution) is said to have an osmolarity of 1 osmolar (1 Osm), and a 1 millimolar (1 m*M*) solution has an osmolarity of 1 milliosmolar (1 mOsm). *The higher the osmolarity of a solution, the lower the concentration of water.* For practical purposes in biological solutions, the identity of the dissolved particle is irrelevant; that is, the concentration of water is effectively the same in a solution of 0.1 Osm glucose, 0.1 Osm sucrose, or 0.1 Osm urea.

To be strictly correct in discussing the concentration of water in various solutions, we would have to use the **molality**, rather than the molarity, of the solutions. Molality is defined as moles of solute per kilogram of solvent. As a result, it takes into account the fact that higher-molecular-weight solutes displace more water per mole of solute than do lower-molecular-weight solutes. That is, a liter of solution containing 1 mole of a large molecule, such as a protein, would contain less water than a liter of solution containing 1 mole of a small molecule, such as urea. Thus, the molality of the protein solution would be higher than the molality of the urea solution, even though both solutions have the same molarity (1 *M*). For our purposes, however, it will be adequate to treat molarity and osmolarity as equivalent to molality and osmolality.

In determining the osmolarity of a solution, we must consider how many dissolved particles result from each molecule of the dissolved substance.

Because glucose, sucrose, and urea molecules do not dissociate when they dissolve, a 0.1 *M* glucose solution is a 0.1 Osm solution. A solution of sodium chloride, however, contains two dissolved particles—a sodium ion and a chloride ion—from each molecule of salt that goes into solution. Thus, a 0.1 *M* NaCl solution is a 0.2 Osm solution. For a more precise definition, interactions among the ions in a solution would need to be factored in, so that the effective osmolarity might be less than that calculated by assuming that all dissolved particles behave independently. For dilute solutions like those usually encountered in cell biology, however, such interactions are weak and can be safely ignored. Thus, for practical purposes we will assume that all dissolved particles act independently in determining the total osmolarity of a solution. Consequently, solutions containing 300 m*M* glucose, 150 m*M* NaCl, 100 m*M* NaCl + 100 m*M* glucose, or 75 m*M* NaCl + 75 m*M* KCl would all have the same total osmolarity—300 mOsm.

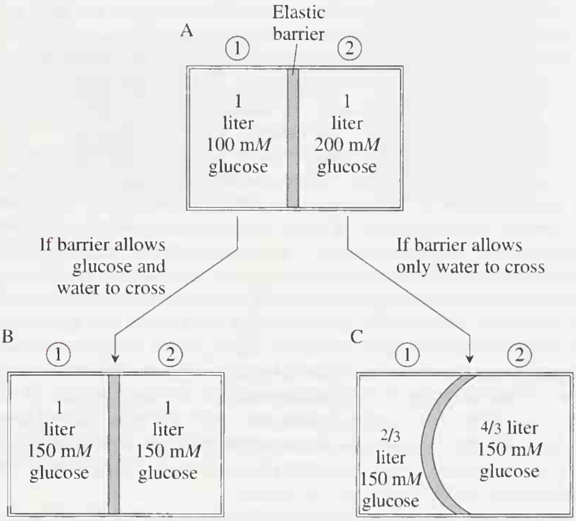
When solutions of different osmolarity come in contact through a water-permeable barrier, water will diffuse across the barrier according to its concentration gradient (that is, from the lower osmolar solution to the higher osmolar solution). This movement of water down its concentration gradient is called osmosis. Consider the example of a container divided into two equal compartments that are filled with glucose solutions, as shown in Figure 3.6A. Imagine that the barrier dividing the container is made of an elastic material, allowing it to stretch freely. If the barrier allows both water and glucose to cross, then water will move from side 1 to side 2, down its concentration gradient, and glucose will move from side 2 to side 1. The movement of water and glucose will continue until their concentrations on the two sides of the barrier are equal. Thus, side 1 gains glucose and loses water, and side 2 loses glucose and gains water until the glucose concentration on both sides is 150 m*M*. No net change occurs in the volume of solution on either side of the barrier, as shown in Figure 3.6B.

If the barrier in Figure 3.6A allows water but not glucose to cross, the outcome will be quite different, however. Once again, water will move down its concentration gradient from side 1 to side 2, but the loss of water will not be offset by a gain of glucose. As water leaves side 1 and accumulates on side 2, the volume of side 2 will increase and the volume of side 1 will decrease. The accumulating water will exert a pressure on the elastic barrier, causing it to expand to the left to accommodate the volume changes (Fig. 3.6C). The osmolarity of side 1 will increase, and the osmolarity of side 2 will decrease. This process will continue until the osmolarities of the two sides are equal—150 mOsm. To prevent these volume changes, we would have to exert a pressure against the elastic barrier from side 1 to keep it from stretching. This pressure must be equal to the pressure moving water down its concentration gradient and would provide a measure of the osmotic pressure gradient across the barrier.

Osmotic balance and cell volume

Consider once again the hypothetical primitive cell, early after the development of a cell membrane. For the cell membrane to perform its job, it must be impermeable to the organic molecules inside the cell. If the extracellular

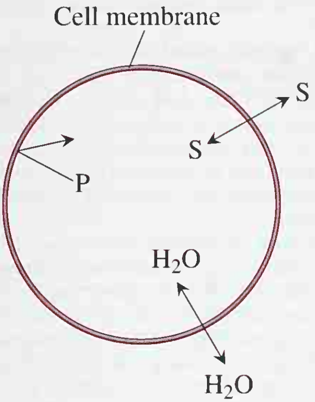
Figure 3.6
The effect of properties of the barrier separating two different glucose solutions (A) on final volumes of the solutions. (B) If the barrier allows both glucose and water to cross, the volumes of the two solutions do not change when equilibrium is reached. (C) If the barrier allows only water to cross, osmolarities of the two solutions are the same at equilibrium, but their final volumes differ.


A
Elastic barrier
①
②
1 liter 100 m*M* glucose
1 liter 200 m*M* glucose
If barrier allows glucose and water to cross
If barrier allows only water to cross
B
①
②
1 liter 150 m*M* glucose
1 liter 150 m*M* glucose
C
①
②
2/3 liter 150 m*M* glucose
4/3 liter 150 m*M* glucose

and intracellular fluids have the same composition except for their internal organic molecules, the cell faces an imbalance of water on the two sides of the membrane. This is shown schematically in Figure 3.7. The solutes that are common to both the ICF and ECF are grouped together and symbolized by *S*. The extra solute inside the cell—that is, the organic molecules (symbolized by *P*, for protein)—produce a lower concentration of water inside the cell than outside it. Put another way, the total osmolarity inside the cell exceeds that found outside the cell. There are two solutes inside the cell, *S* and *P*, and only one outside. Consequently, water will continue to enter the cell until the osmolarity on the two sides of the membrane is identical. Because the volume of the sea where the primitive organism resides is essentially infinite relative to the volume of a cell, it can be treated as constant. As a result, this end point could be reached only when the internal concentration of organic solutes is zero—and the volume of the cell must be infinite. Real cell membranes are not infinitely elastic, however. Thus, water will enter the cell, causing it to swell, until the membrane ruptures and the cell bursts.

Figure 3.7

A simple model cell containing organic molecules, *P*. The extracellular fluid is a solution of solute, *S*, in water. Both water and *S* can cross the cell membrane, but *P* cannot.



It is convenient to summarize this situation in equation form. If a substance is at diffusion equilibrium across a cell membrane, there is no net movement of that substance across the membrane. For any solute, *S*, that can cross the cell membrane, diffusion equilibrium will be reached when

$$[S]_i = [S]_o \tag{3.1}$$

The square brackets indicate the concentration of a substance, and the subscripts *i* and *o* refer to the inside and outside of the cell, respectively. Thus, for water to reach equilibrium, we would expect that

$$[S]_i + [P]_i = [S]_o \tag{3.2}$$

This equation simply says that, at equilibrium, the total osmolarity inside the cell must be the same as the total osmolarity outside the cell. For the cell shown in Figure 3.7, diffusion equilibrium will be reached only when the concentrations of all substances that can cross the membrane (in this case, *S* and water) are equal both inside and outside the cell. Thus, Equations (3.1) and (3.2) must be true simultaneously, which can occur only if $[P]_i$ is zero.

Answers to the problem of osmotic balance

What solutions exist to this apparently fatal problem? Three basic strategies have developed in different types of cells.

First, the problem could be eliminated by making the cell membrane impermeable to water. This solution is difficult to achieve, however, and is rarely applied to the problem of osmotic balance. Certain kinds of epithelial cells, however, have achieved very low permeability to water.

A second, more commonly encountered strategy likely represented the initial solution to the problem. The basic idea is to use brute force—that is, to build an inelastic wall around the cell membrane to physically prevent the cell from swelling. This solution is employed by both bacteria and plants.

The third strategy, which is found in animal cells, achieves osmotic balance by making the cell membrane impermeable to selected extracellular solutes. This solution balances the concentration of nonpermeating molecules inside the cell with the same concentration of nonpermeating solutes outside the cell. To see how this strategy works, let us consider some examples using a simplified model animal cell whose membrane is permeable to water. Suppose that the model cell contains only one solute: nonpermeating protein molecules, *P*, dissolved in water at a concentration of 0.25 M. We will then perform a series of experiments on this model cell by placing it in various extracellular fluids and deducing what would happen to its volume in each case. Assume that the initial volume of the cell is one-billionth of a liter (1 nanoliter, or 1 nL) and that the volume of the extracellular fluid is always infinite. This latter assumption means that the concentration of extracellular solutes does not change during the experiments.

In the first experiment, the cell is placed in a 0.25 M solution of sucrose, which does not cross cell membranes (Fig. 3.8A). In this situation, only water can cross the cell membrane. For water to be at equilibrium, the internal osmolarity must equal the external osmolarity, or

$$[P]_i = [\text{sucrose}]_o \tag{3.3}$$

Because the internal and external osmolarities are both 0.25 Osm, this condition is met. No net diffusion of water will occur, and cell volume will not change.

In the second experiment (Fig. 3.8B), the cell is placed in 0.125 M sucrose. Again, only water can cross the membrane, and Equation (3.3) must be satisfied if equilibrium is to be achieved. In 0.125 M sucrose, the internal osmolarity exceeds the external osmolarity, and water will enter the cell until the internal osmolarity falls to 0.125 M. This will happen when the cell volume doubles to reach 2 nL. (As an extension of these two experiments, consider what the equilibrium cell volume would be if we placed the cell in 0.5 M sucrose rather than 0.125 M sucrose.)

In these two experiments, water will reach equilibrium if the concentration of impermeant extracellular solute equals the concentration of impermeant internal solute. To see that the external solute must not be able to cross the cell membrane, consider another example. In this case, the model cell is placed in 0.25 M urea, rather than sucrose (Fig. 3.8C). Unlike sucrose, urea can cross the cell membrane. Consequently, we must take into account both urea and water in determining diffusion equilibrium. In equation form, equilibrium will be reached when two relations hold:

$$[\text{urea}]_i = [\text{urea}]_o \tag{3.4}$$

$$[\text{urea}]_i + [P]_i = [\text{urea}]_o \tag{3.5}$$

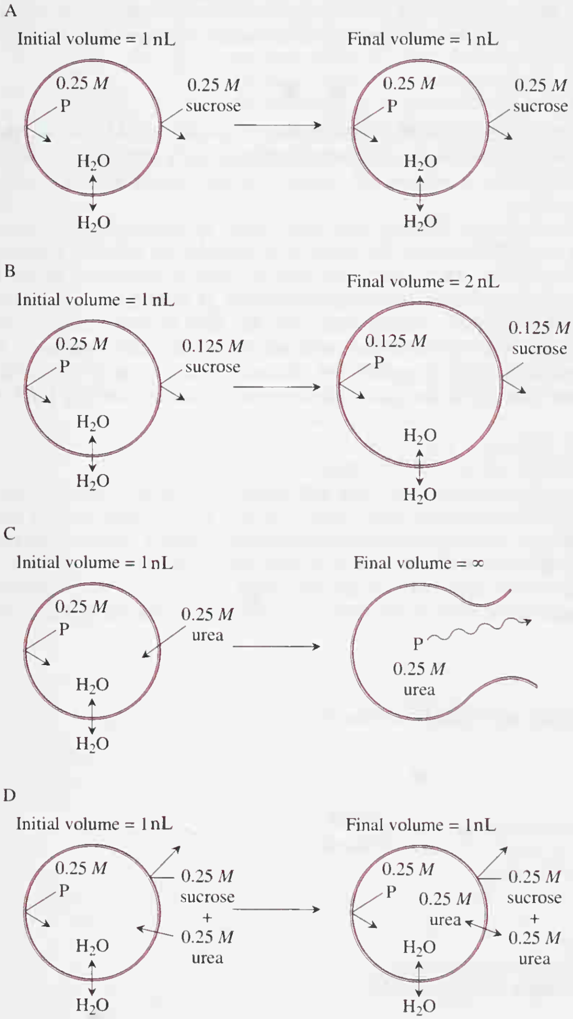
Because the external volume is infinite, $[\text{urea}]_o$ will be 0.25 M at equilibrium. According to Equation (3.4), $[\text{urea}]_i$ will also be 0.25 M. Thus, Equations (3.4) and (3.5) require that $[P]_i$ be zero at equilibrium. Thus, the equilibrium volume is infinite, and the cell will swell until it bursts. Qualitatively, when the cell is first placed in 0.25 M urea, no net movement of water across the membrane will occur, as the internal and external osmolarities are both 0.25 Osm. As urea enters the cell down its concentration gradient, however, internal osmolarity rises in concert with the accumulation of urea. Water will then begin to enter the cell down its concentration gradient. The cell swells until it bursts. Thus, an extracellular solute that can cross the cell membrane cannot help a cell achieve osmotic balance.

In another interesting experiment, the model cell is placed in a mixture of 0.25 M urea and 0.25 M sucrose (Fig. 3.8D). The equilibrium for urea will once again be given by Equation (3.4), and water will be at equilibrium when

$$[\text{urea}]_i + [P]_i = [\text{urea}]_o + [\text{sucrose}]_o \tag{3.6}$$

Equations (3.4) and (3.6) will both be satisfied when $[P]_i = 0.25$ M, which is the initial condition. Therefore, in this example, the cell volume at diffusion equilibrium will be the normal volume, 1 nL. Even if some extracellular

Figure 3.8
The effects of various extracellular fluids on the volume of a simple model. (A) The ECF contains an impermeant solute (sucrose), and the osmolarity is the same as that inside the cell. (B) The ECF contains an impermeant solute, and the osmolarity is lower than that inside the cell. (C) The ECF contains a permeant solute (urea), and external and internal osmolarities are equal. (D) The ECF contains a mixture of permeant and impermeant solutes.



solutes proves able to cross the cell membrane, the presence of a nonpermeating external solute at the same concentration as the nonpermeating internal solute allows the cell to achieve diffusion equilibrium for water and to maintain its volume. Animal cells use this strategy to avoid bursting, with the impermeant extracellular solute being sodium (see Table 3.1).

In all of the examples of osmotic equilibrium given here, we arrived at the answer by using just one rule: *For each permeating substance (including water), the inside concentration must equal the outside concentration at equilibrium.*

Tonicity

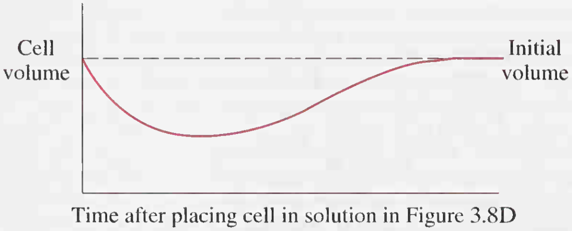
In the examples given in Figure 3.8, 0.25 M sucrose and 0.25 M urea had the same osmolarity (0.25 Osm), but produced dramatically different effects on cell volume. In 0.25 M sucrose, cell volume did not change; in 0.25 M urea, the cell exploded.

To account for the differing biological effects of solutions of the same osmolarity, we will introduce the concept of **tonicity**. An **isotonic** solution has no final effect on cell volume; a **hypotonic** solution causes cells to swell; and a **hypertonic** solution causes cells to shrink at equilibrium. Thus, the 0.25 M sucrose solution was isotonic, and the 0.25 M urea solution was hypotonic. Note that an isotonic solution must have the same osmolarity as the fluid inside the cell at equilibrium. Having the same osmolarity as the intracellular fluid does not guarantee, however, that an external fluid is isotonic.

Time-course of volume changes

In our discussion of maintenance of cell volume, we have considered only the final, equilibrium effect of a solution on cell volume and ignored any transient effects. To analyze such transient effects, consider what happens to the model cell immediately after it is placed in a solution of 0.25 M urea + 0.25 M sucrose (Fig. 3.9). Initially, the osmolarity outside (0.5 Osm) is greater than the osmolarity inside (0.25 Osm), and water leaves the cell as it diffuses

Figure 3.9
The time-course of cell volume when the model cell is placed in solution D from Figure 3.8.



down its concentration gradient. Urea begins, however, to diffuse into the cell down its concentration gradient. Thus, the internal osmolarity rises in response to the increase in $[\text{urea}]_i$ and the loss of intracellular water. The water leakage slows and finally stops when $[P]_i + [\text{urea}]_i = 0.5$ M; at that point, internal and external osmolarities are equal. However, $[P]_i$ then exceeds its initial value (0.25 M) because of the reduction in cell volume, and thus $[\text{urea}]_i$ is less than 0.25 M. As a result, urea continues to enter the cell in an effort to reach its own diffusion equilibrium, and the internal osmolarity rises above 0.5 Osm. In turn, water enters the cell and volume begins to increase. This situation continues until the final equilibrium state governed by Equations (3.4) and (3.6) is reached.

What would you expect the time-course of cell volume to be if the model cell were placed in an infinite volume of a solution of 0.5 M urea?

SUMMARY OF OSMOTIC BALANCE

For animal cells to survive, they must regulate the movement of water across the plasma membrane. Given that proteins and other organic constituents of the ICF cannot be allowed to cross the membrane, diffusion of water becomes a problem. Animal cells have solved this problem by excluding a compensating extracellular solute, sodium ions. (Later chapters will discuss this exclusion of Na^+ in detail.)

Diffusion equilibrium is reached when internal and external concentrations are equal for all substances that can cross the membrane. For uncharged substances, the influence of electrical force on the equilibrium state can be ignored. The solutes of the ICF and ECF of real cells do, however, carry a net electrical charge. In chapter 4, we will consider the roles played by electric fields in the movements of these charged substances across the membranes of animal cells.

4

Origin of Electrical Membrane Potential

In chapter 3, we examined the factors that influence the distribution of water across the plasma membrane and the strategies by which cells can attain osmotic equilibrium. For clarity, our examples used only uncharged particles. A glance at Table 3.1, however, shows that the solutes of both ICF and ECF are all electrically charged. For charged particles, movement across the membrane will be determined not only by diffusional force, but also by the electrical potential across the membrane. We will now consider how cells can achieve equilibrium in a situation in which both diffusional and electrical forces must be taken into account.

MEMBRANE POTENTIAL: IONIC EQUILIBRIUM

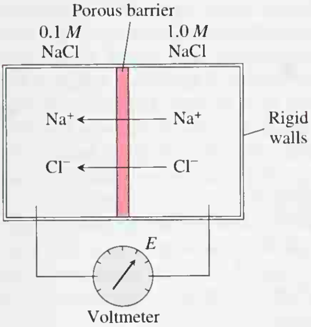
To illustrate the important principles that apply to ionic equilibrium, we will work through a series of examples that increase in both complexity and similarity to real animal cells. At the end of the series, we will see how a model cell, with internal and external compositions like those given in Table 3.1, could achieve electrical and chemical equilibrium. In the second part of this chapter, we will see how this equilibrium model of the electrochemical state of cells differs from the situation in real animal cells, as real cells must expend energy to maintain the distribution of ions across their plasma membranes.

Diffusion potential

The names **cation** for a positively charged particle and **anion** for a negatively charged particle arise from the observation that dissolved positively charged particles accumulate around a wire connected to the negative pole (cathode) of a battery and that dissolved negatively charged particles are attracted to a wire connected to the positive pole (anode). The battery creates a gradient of electrical potential (a voltage gradient) in the solution, which then influences the movement of ions within the solution. Thus, the distribution of ions in a solution depends on the presence of an electric field in that solution. Conversely, a differential distribution of ions in a solution gives rise to a voltage gradient in the solution. As an example of how an electrical potential can arise from spatial differences in the distribution of ions, we will consider the origin of diffusion potentials.

Diffusion potentials arise when two or more ions are moving down a concentration gradient. Consider the situation illustrated in Figure 4.1, in

Figure 4.1
A schematic diagram of an apparatus for measuring diffusion potential. The voltmeter is wired to measure the electrical voltage difference across the barrier separating the two salt solutions.



which a rigid container is divided into two compartments by a porous barrier. The left compartment contains a 0.1 M NaCl solution, and the right compartment contains a 1.0 M NaCl solution. The porous barrier allows Na^+, Cl^-, and water to pass through, but the rigid walls prevent the compartment volume from changing. Thus, water cannot move, and osmotic factors can be neglected for the moment. Both Na^+ and Cl^- will move down their concentration gradients from right to left until their concentrations are equal in both compartments. In aqueous solution, Na^+ and Cl^- do not move at the same rate; Cl^- is more mobile and moves from right to left more quickly than Na^+. This difference emerges because ions dissolved in water carry with them a loosely associated "cloud" of water molecules. Na^+ must drag along a larger cloud than Cl^-, causing it to move more slowly.

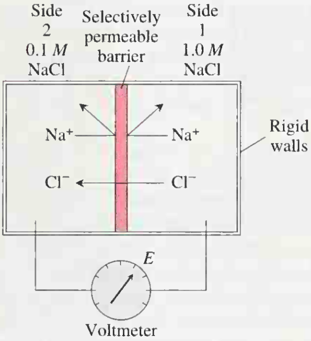
In our example, the concentration of Cl^- on the left side of the compartment will increase faster than the concentration of Na^+. In other words, the left compartment will contain more negative charges than positive charges, and a voltmeter connected between the two sides would record a voltage difference, *E*, across the barrier, with the left compartment appearing negative with respect to the right compartment. This voltage difference is the diffusion potential. Because the excess negative charges on the left repel Cl^- and attract Na^+, the electrical potential across the barrier retards movement of Cl^- and speeds up movement of Na^+. The diffusion potential continues to build up until the electrical effect on the ions exactly counteracts the greater mobility of Cl^-, and the two ions cross the barrier at the same rate.

Voltage is also called electromotive force, a name that emphasizes voltage's role in driving the movement of electrical charges through space. Thus, voltage can be envisioned as a pressure driving charges in a particular direction, just as the pressure in a water pipe forces water out through a faucet when you open the valve. Unlike the pressure in a hydraulic system, however, a voltage gradient can move charges in opposing directions, depending on the polarity involved. Thus, the negative pole of a battery simultaneously attracts positively charged particles and repels negatively charged particles.

Equilibrium potential: the Nernst equation

The diffusion potential example given in Figure 4.1 does not describe an equilibrium condition, but rather a transient situation that occurs only when a net diffusion of ions across the barrier takes place. Equilibrium would be achieved in this case only when $[Na^+]$ and $[Cl^-]$ are the same in both compartments. At that point, no concentrational force would be available to support net diffusion of either Na^+ or Cl^- across the membrane and no electrical potential would occur across the barrier. Under what conditions might a steady-state electrical potential be found at equilibrium? Consider a small modification to the previous example (Fig. 4.2). All aspects of the set-up remain the same, except that the barrier between the two compartments of

Figure 4.2
A schematic diagram of apparatus for measuring the equilibrium, or Nernst, potential for a permeant ion. At equilibrium, a steady-state electrical potential (the equilibrium potential) will exist across the selectively permeable barrier, separating the two salt solutions.



the box is selectively permeable to Cl^-—that is, Na^+ cannot cross. Once again, we assume that the box has rigid walls so that we can ignore movement of water.

The analysis of this example is similar to that of the diffusion potential example, except that the "mobility" of Na^+ is reduced effectively to zero by the barrier's permeability characteristics. Chloride ions will move down their concentration gradient from compartment 1 to compartment 2, but no positive charges will accompany them and negative charges will quickly build up in compartment 2. Thus, the voltmeter will record an electrical potential across the barrier, with side 2 appearing negative with respect to side 1. Because only Cl^- can cross the barrier, equilibrium will be reached when net movement of chloride across the barrier ceases. This point occurs when the electrical force driving Cl^- out of compartment 2 exactly balances the concentrational force driving Cl^- out of compartment 1. At equilibrium, one chloride ion moves from side 1 to side 2 down its concentration gradient for every chloride ion that moves from side 2 to side 1 down its electrical gradient. Once equilibrium is achieved, there will be no further change in $[Cl^-]$ in the two compartments and no further change in the electrical potential.

Equilibrium for an ion is determined not only by concentrational forces but also by electrical forces. *Movement of an ion across a cell membrane is determined by two factors: the concentration gradient for that ion across the membrane and the electrical potential difference across the membrane.* Because these ideas are used extensively in later chapters, the remainder of this chapter is devoted to the application of these principles in simple model situations and real cells.

What would be the measured value of the voltage across the barrier at equilibrium in Figure 4.2? The answer to this quantitative question is provided by Equation (4.1), which is called the **Nernst equation** after the physical chemist who derived it:

$$E_{Cl} = \left(\frac{RT}{ZF}\right)\ln\left(\frac{[Cl^-]_1}{[Cl^-]_2}\right) \tag{4.1}$$

In this equation, E_{Cl} is the voltage difference between sides 1 and 2 at equilibrium, R is the gas constant, T is the absolute temperature, Z is the valence of the ion (-1 for chloride), F is Faraday's constant, "ln" is the symbol for the natural (base e) logarithm, and $[Cl^-]_1$ and $[Cl^-]_2$ are the chloride concentrations in compartments 1 and 2.

The value of the electrical potential given by Equation (4.1) is called the **equilibrium potential**, or **Nernst potential**, for the ion. For example, in Figure 4.2, the permeant ion is chloride and the electrical potential, E_{Cl}, across the barrier is called the chloride equilibrium potential. If this barrier allowed Na^+ to cross rather than Cl^-, Equation (4.1) would again apply, except that $[Na^+]_1$ and $[Na^+]_2$ would be used instead of $[Cl^-]$, and the valence would be $+1$ instead of -1. If sodium were the permeant ion, the resulting potential, E_{Na}, would be called the sodium equilibrium potential. *The Nernst equation applies only to one ion at a time and only to ions that can cross the barrier.*

Appendix A provides a derivation of Equation (4.1), which results from the realization that the total change in energy encountered by an ion in crossing the barrier must be zero at equilibrium. If the change in energy were not zero, a net force would drive the ion in some direction, and the ion would not be at equilibrium. Two important sources of energy change are involved in crossing the barrier shown in Figure 4.2: the electrical field and the concentration gradient. Nernst arrived at his equation by setting the sum of the concentrational and electrical energy changes across the barrier to zero.

In biology, we usually work with a simplified form of Equation (4.1):

$$E_{Cl} = \left(\frac{58\ \text{mV}}{Z}\right)\log\left(\frac{[\text{Cl}^-]_1}{[\text{Cl}^-]_2}\right) \tag{4.2}$$

The simplification arises from converting from natural to base 10 logarithms, evaluating (RT/F) at standard room temperature (20°C), and expressing the result in millivolts (mV). This conversion yields the constant 58 mV seen in Equation (4.2). From the simplified Nernst equation, it can be seen that E_{Cl} in Figure 4.2 would be −58 mV. That is, in crossing the barrier from side 1 to side 2, a potential change of 58 mV would be encountered, with side 2 appearing negative with respect to side 1. This situation is expected because chloride ions, and thus negative charges, are accumulating on side 2. If the barrier were selectively permeable to Na^+ rather than Cl^-, the voltage across the barrier would be given by E_{Na} (+58 mV, given the values in Figure 4.2).

What would be the equilibrium potential for chloride given the set-up in Figure 4.2 if the concentration of NaCl was 1.0 M on both sides of the barrier? (Hint: The concentration gradient would be zero.)

The principle of electrical neutrality

In arriving at −58 mV for the chloride equilibrium potential in Figure 4.2, we used 1.0 M and 0.1 M for $[\text{Cl}^-]_1$ and $[\text{Cl}^-]_2$. These values represent the initial concentrations in the two compartments, even though our qualitative analysis noted that Cl^- moved from compartment 1 to 2, producing an excess of negative charge in compartment 2 and generating the electrical potential. This situation would seem to suggest that $[\text{Cl}^-]$ changes from its initial value, invalidating our sample calculation. Initial concentrations can be used, however, because the increment in the electrical gradient caused by the movement of a single charged particle from compartment 1 to 2 is much larger than the decrement in concentration gradient resulting from movement of that same particle. Thus, *only a very small number of charges must accumulate to counteract even a large concentration gradient.*

In Figure 4.2, for example, if the volume of each compartment were 1 mL and the barrier between compartments consisted of 1 cm^2 of the material found in cell membranes, fewer than one-billionth of the chloride ions of side 1 would need to move to side 2 to reach the equilibrium potential of −58 mV. (The basis of this calculation is explained below.) Clearly, such a small change in concentration would produce an insignificant difference in the result calculated from Equation (4.2), and we can safely ignore the movement of chloride necessary to achieve equilibrium.

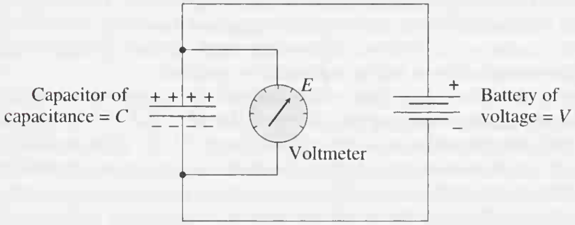
This consideration leads to an important concept, called the **principle of electrical neutrality.** It states that, *under biological conditions, the bulk concentration of cations within any compartment must equal the bulk concentration of anions in that compartment.* This approximation is acceptable because the number of charges necessary to reach transmembrane potentials of the magnitude encountered in biology is insignificant compared with the total number of cations and anions in the intracellular and extracellular fluids.

The cell membrane as an electrical capacitor

In this section, we will consider how we calculated the number of charges necessary to produce the equilibrium membrane potential of −58 mV in the preceding section. In the calculation, we treated the barrier between the two compartments as an electrical capacitor, which is a charge-storing device consisting of two conducting plates separated by an insulating barrier. In Figure 4.2, the two conducting plates are the salt solutions in the two compartments, and the barrier is the insulator. In a real cell, the ICF and ECF are the conductors, and the lipid bilayer of the plasma membrane is the insulating barrier.

When a capacitor is hooked up to a battery (Fig. 4.3), the battery's voltage causes electrons to leave one conducting plate and to accumulate on the other plate. This process continues until the resulting voltage gradient across the capacitor equals the voltage of the battery. Basic physics tells us that the amount of charge, q, stored on the capacitor at that time will be given by $q = CV$, where V is the voltage of the battery and C is the **capacitance** of the capacitor. This capacitance is directly proportional to the area of the plates (bigger plates can store more charge) and inversely proportional to the distance separating the two plates. It also depends on the characteristics of the insulating material between the plates—in the case of cells, the lipid

Figure 4.3
When a battery is connected to a capacitor, charge accumulates on the capacitor until the voltage across the capacitor equals the voltage of the battery.



plasma membrane. The unit of capacitance is the farad (F). A 1 F capacitor can store 1 coulomb of charge when hooked up to a 1 V battery. Biological membranes, like the plasma membrane, have a capacitance of 10^{-6} F (that is, 1 microfarad, or μF) per cm^2 of membrane area.

If the barrier in Figure 4.2 consisted of 1 cm^2 of cell membrane, it would have a capacitance of 10^{-6} F. From the equation $q = CV$, it follows that an equilibrium potential of −58 mV would store 5.8×10^{-8} coulomb of charge on the barrier. The charge on the membrane barrier in Figure 4.2 is carried by ions, not by electrons as in Figure 4.3. To calculate the total number of excess anions on side 2 of the barrier at equilibrium, we must convert from coulombs of charge to moles of ion. To do this, we divide the number of coulombs on the barrier by Faraday's constant (approximately 10^5 coulombs per mole of monovalent ion), yielding 5.8×10^{-13} mole or approximately 3.5×10^{11} chloride ions moving from side 1 to side 2 in Figure 4.2. If the volume of each compartment were 1 mL, then side 2 would contain approximately 6×10^{20} chloride and sodium ions. Thus, we conclude that fewer than one-billionth of the chloride ions in side 1 cross to side 2 to produce the equilibrium voltage across the barrier.

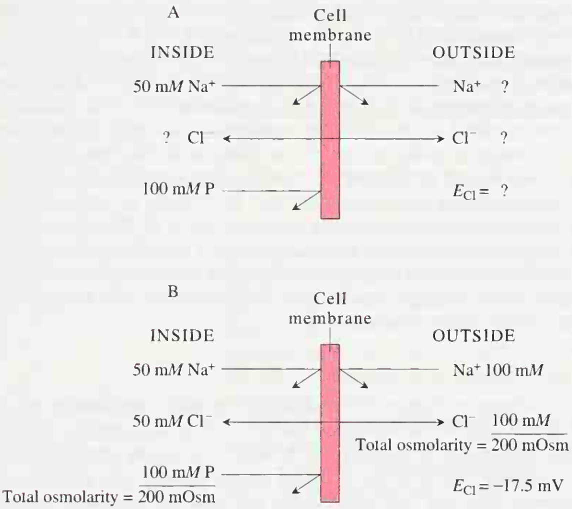
Incorporating osmotic balance

The example shown in Figure 4.2 illustrates how ionic equilibrium can be reached and how the Nernst equation can be used to calculate the value of the membrane potential at equilibrium. However, the simple situation in the example is not very similar to the situation in real animal cells. Animal cells are not enclosed in a box with rigid walls, and thus we must take osmotic balance into account. Consider an example in which the rigid walls are removed, so that osmotic balance must be achieved to reach equilibrium (Fig. 4.4A). In addition, an impermeant intracellular solute, *P*, has been added. For now, *P* has no charge; the effect of adding a charge on the intracellular organic solute will be considered later in this chapter.

Figure 4.4A assumes that the model cell contains 50 mM Na$^+$ and 100 mM *P*. What concentrations of the other intracellular and extracellular solutes are needed for the model cell to reach equilibrium? The principle of electrical neutrality tells us that, for practical purposes, the concentrations of cations and anions within any compartment are equal. Thus, because *P* is assumed to have no charge, $[\mathrm{Cl}^-]_i = [\mathrm{Na}^+]_i = 50$ mM. For osmotic balance, the external osmolarity must equal the internal osmolarity (200 mOsm). The principle of electrical neutrality again requires that $[\mathrm{Na}^+]_o = [\mathrm{Cl}^-]_o$. This requirement, together with the requirement for osmotic balance, can be satisfied if $[\mathrm{Na}^+]_o = [\mathrm{Cl}^-]_o = 100$ mM. The model cell (see Fig. 4.4A) can, therefore, reach equilibrium if the concentrations of intracellular and extracellular solutes are as shown in Figure 4.4B. At this equilibrium, the electrical potential across the membrane of the model cell (the membrane potential, E_m) would be given by the Nernst equation for chloride:

$$E_m = E_{Cl} = -58\ \mathrm{mV}\log\left(\frac{[\mathrm{Cl}^-]_o}{[\mathrm{Cl}^-]_i}\right) = -17.5\ \mathrm{mV}$$

Figure 4.4
A model cell in which both osmotic and electrical factors must be considered at equilibrium.



Donnan equilibrium

The example in Figure 4.4B indicates how we could construct a model cell that reaches osmotic and ionic equilibrium simultaneously. This situation still differs greatly from that seen in real animal cells, however. In real cells, the principal internal cation is K^+, not Na^+. Also, the ECF contains potassium, and the cell membrane is permeable to both K^+ and Cl^-. Thus, two ions can cross the membrane: K^+ and Cl^-. To achieve equilibrium, the electrical potential across the cell membrane must exactly balance the concentration gradients for both K^+ and Cl^-. Because the membrane potential can have only one value, this equilibrium condition will be satisfied only when the equilibrium potentials for Cl^- and K^+ are equal. In equation form, this condition can be written as

$$E_K = 58\text{ mV}\log\left(\frac{[K^+]_o}{[K^+]_i}\right) = E_{Cl} = -58\text{ mV}\log\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right)$$

In this equation, the minus sign on the far right arises from the fact that the valence of chloride is −1. Canceling 58 mV from this equation leaves

$$\log\left(\frac{[K^+]_o}{[K^+]_i}\right) = -\log\left(\frac{[Cl^-]_o}{[Cl^-]_i}\right) \tag{4.3}$$

The minus sign on the right side can be moved inside the parentheses of the logarithm to yield $\log([Cl^-]_i/[Cl^-]_o)$. Thus, equilibrium will be reached when

$$\left(\frac{[K^+]_o}{[K^+]_i}\right) = \left(\frac{[Cl^-]_i}{[Cl^-]_o}\right) \tag{4.4}$$

This equilibrium condition, which is called the **Donnan** (or **Gibbs-Donnan**) **equilibrium**, specifies the conditions that must be met if two ions that can cross a cell membrane are simultaneously to be at equilibrium across that membrane. Equation (4.4) is usually written in a slightly rearranged form as the product of concentrations:

$$[K^+]_o[Cl^-]_o = [K^+]_i[Cl^-]_i \tag{4.5}$$

Thus, for a Donnan equilibrium to hold, *the product of the concentrations of the permeant ions outside the cell must be equal to the product of the concentrations of those two ions inside the cell.*

To see how the Donnan equilibrium might apply in an animal cell, consider an example in which a model cell containing K^+, Cl^-, and P is placed in ECF containing Na^+, K^+, and Cl^- (Fig. 4.5A). As an exercise, we will calculate the values of all concentrations at equilibrium, assuming that $[Na^+]_o$ is 120 mM and $[K^+]_o$ is 5 mM. From the principle of electrical neutrality, $[Cl^-]_o$ must be 125 mM. In addition, because P is assumed to be uncharged, the principle of electrical neutrality requires that $[K^+]_i$ must equal $[Cl^-]_i$. Because two ions—K^+ and Cl^-—can cross the membrane, the defining relation for a Donnan equilibrium shown in Equation (4.5) must be obeyed. Thus, if the model cell (see Fig. 4.5A) is to reach equilibrium, $[K^+]_i[Cl^-]_i$ must equal $[K^+]_o[Cl^-]_o$, which is 5 × 125, or 625 mM^2. Because $[K^+]_i = [Cl^-]_i$, the Donnan condition reduces to $[K^+]_i2 = 625$ mM^2; thus, $[K^+]_i$ and $[Cl^-]_i$ must be 25 mM at equilibrium. For osmotic balance, the internal osmolarity must equal the external osmolarity, which is 250 mOsm. Thus, $[P]_i$ must be 200 mM for the model cell to be at equilibrium. The results of this example are summarized in Figure 4.5B, which represents a model cell at equilibrium.

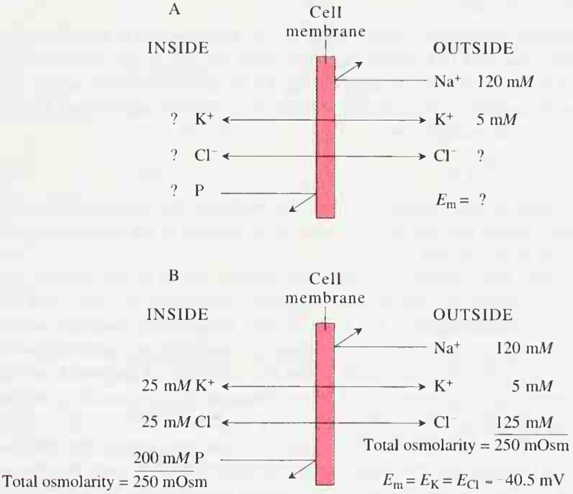
What would be the membrane potential of this equilibrated model cell? The Nernst equation—Equation (4.2)—tells us that the membrane potential for a cell at equilibrium with $[K^+]_o = 5$ mM and $[K^+]_i = 25$ mM is approximately −40.5 mV, with the inside appearing negative. You should satisfy yourself that the Nernst equation for chloride yields the same value for the membrane potential.

A model cell that looks like a real animal cell

The model cell shown in Figure 4.5B still lacks many features of real animal cells. For instance, the internal organic molecules are charged (see Table 3.1), and this charge must be considered in the balance between cations and anions required by the principle of electrical neutrality. Recall that the category of internal anions, A^-, actually represents a diverse group of molecules, including proteins, charged amino acids, and sulfate and phosphate ions. Some of these substances carry a single negative charge, others bear two negative charges, and some carry even three net negative charges. Taken as a

Figure 4.5

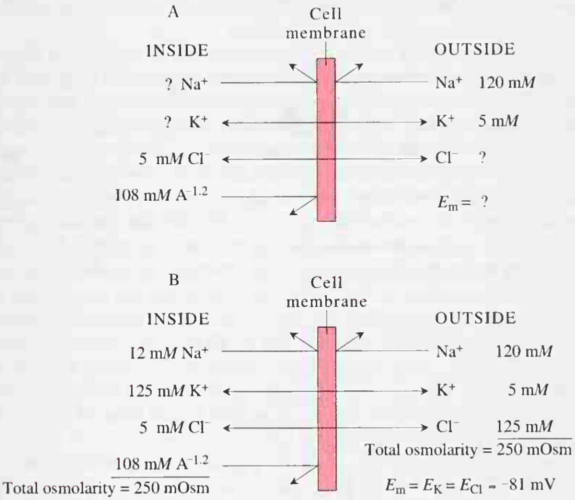
An example of a model cell at Donnan equilibrium. The cell membrane is permeable to both potassium and chloride.



group, however, the average charge per molecule is slightly greater than −1.2. Thus, the internal impermeant anions can be represented as $A^{1.2-}$.

In addition, the current model cell lacks Na^+ inside the cell, while real ICF does contain a small amount of sodium. Addition of these complicating factors leads to a new model cell (Fig. 4.6A) that contains all of the constituents shown in Table 3.1. If this cell is to reach equilibrium, what concentrations of the various ions in ECF and ICF would be required, and what would the transmembrane potential be? To begin, we will take some values from Table 3.1 and determine the remaining parameters necessary for the cell to be at equilibrium. Assume that $[K^+]_o = 5$ mM, $[Na^+]_o = 120$ mM, $[Cl^-]_i = 5$ mM, and $[A^{1.2-}]_i = 108$ mM. (We could actually calculate the concentration of A from the other parameters. For mathematical simplicity, however, we will assume that it is known initially.) Because Cl^- is the sole external anion, the principle of electrical neutrality requires that $[Cl^-]_o$ be 125 mM. Both K^+ and Cl^- can cross the membrane, so that the conditions for a Donnan equilibrium—Equation (4.5)—must be satisfied. Thus, $[K^+]_i = 125$ mM. The equilibrated value of $[Na^+]_i$ can then be obtained from the requirements for osmotic balance; $[Na^+]_i$ must be 12 mM if internal and external osmolarities are equal. From the Nernst equation for either Cl^- or K^+, the membrane potential at equilibrium can be determined to be approximately −81 mV.

Figure 4.6
A realistic model cell that is at both electrical and osmotic equilibrium. The compositions of ECF and ICF for this equilibrated model cell are the same as for a typical mammalian cell (see Table 3.1).



The equilibrium values for this model cell are shown in Figure 4.6B. Note that the concentrations of all intracellular and extracellular solutes are the same for the model cell and for real mammalian cells (see Table 3.1). We arrived at the values in Figure 4.6B by assuming that the cell was in equilibrium; this assumption implies that the real cell, which has the same ECF and ICF, is also at equilibrium. Thus, the model cell—and by extension the real cell—will remain in the state summarized in Figure 4.6B without expending any metabolic energy. From this viewpoint, the animal cell is a beautiful example of efficiency, existing at perfect ionic and osmotic equilibria, in harmony with its electrochemical environment. Unfortunately, the model cell is not an accurate representation of the situation in real animal cells. *Real cells are not at equilibrium and must expend metabolic energy to maintain the status quo.*

The sodium pump

The model in Figure 4.6B was considered to be an accurate description of real animal cells for some time. Problems arose, however, when it became apparent that real cells are permeable to sodium. Permeability to sodium, however, would be catastrophic for the model cell. If sodium can cross the membrane, then all extracellular solutes can cross the membrane. Recall from chapter 2 that cells placed in ECF containing only permeant solutes (like the urea example in Figure 3.8C) eventually swell and burst. The cornerstone of the strategy employed by animal cells to achieve osmotic balance is that their cell membranes must exclude an extracellular solute to balance the impermeant organic solutes inside the cells. Sodium ions played that role for the model cell.

How can the permeability of the plasma membrane to sodium be reconciled with the requirement for osmotic balance? An answer was suggested by experiments that demonstrated the sodium permeability of the cell membrane. In these experiments, red blood cells were incubated in an external medium containing radioactive sodium ions. After the cells were removed from the radioactive medium and washed thoroughly, they remained radioactive, indicating that they had taken up some of the sodium. Thus, the plasma membrane appeared to be permeable to sodium. In addition, the radioactive cells slowly lost their radioactive sodium when incubated in normal ECF. This latter observation was surprising because the concentration gradient and the electrical gradient for sodium are both directed inward; neither would tend to move sodium out of the cell. Further, the rate of this loss of radioactive sodium from the cell interior was slowed dramatically by cooling the cells, indicating that a source of energy other than simple diffusion was being tapped to "pump" sodium out of the cell against its concentrational and electrical gradients. This energy source involves metabolic energy in the form of the phosphate compound adenosine triphosphate (ATP).

The active pumping of sodium out of the cell effectively prevents sodium from accumulating intracellularly as it leaks in down its concentration and electrical gradients. Thus, while sodium can cross the membrane, it is actively expelled at a rate sufficiently high to counterbalance the inward leak. The net result is that sodium behaves osmotically as though it cannot cross the membrane. This mechanism differs fundamentally from the situation in the model cell (see Fig. 4.6B). The model required no energy input to maintain its equilibrium. In contrast, real animal cells exist in a finely balanced steady state, characterized by no net movement of ions across the cell membrane, but requiring the expenditure of metabolic energy.

Metabolic inhibitors, such as cyanide or dinitrophenol, prevent the pumping of sodium out of the cell and cause cells to gain sodium and swell. If ATP is added, the pump can operate again and will extrude the accumulated sodium. Similarly, other manipulations that reduce the rate of ATP production, such as cooling, spur sodium accumulation and increased cell volume. Experiments of this type have demonstrated ATP's role in the active extrusion of sodium and the maintenance of cell volume. In addition, the mechanism of the sodium pump has been studied biochemically. The pump itself consists of a particular kind of membrane-associated protein molecule that can bind both sodium ions and ATP at the intracellular face of the membrane. The protein then acts as an enzyme to cleave one of the high-energy phosphate bonds of the ATP molecule, using the released energy to drive the bound sodium out across the membrane by a process that is not yet completely understood.

The action of the sodium pump also requires potassium ions in the ECF. Binding of K^+ to a part of the protein on the outer surface of the cell membrane allows the protein to return to the configuration in which it can bind another ATP molecule and sodium ions at the inner surface of the membrane. The potassium bound on the outside is released again on the inside of the cell. In this way, the protein molecule acts as a bidirectional pump, carrying sodium out across the membrane and potassium in. Thus, the sodium pump is more correctly referred to as the sodium–potassium pump. It can be envisioned as a shuttle carrying Na^+ out across the membrane, releasing it in the ECF, then carrying K^+ in across the membrane, and releasing it in the ICF. Because the pump molecule splits ATP and binds both sodium and potassium ions, biochemists refer to this membrane-associated enzyme as a Na^+-K^+ ATPase.

SUMMARY OF IONIC EQUILIBRIUM

The movement of charged substances across the plasma membrane is governed not only by the concentration gradient across the membrane, but also by the electrical potential across the membrane. Equilibrium for an ion across the membrane is reached when the electrical gradient exactly balances that ion's concentration gradient. The Nernst equation expresses this equilibrium condition quantitatively, giving the value of the membrane potential that will exactly balance a given concentration gradient.

If more than one ion can cross the cell membrane, both can be at equilibrium only if the Nernst (or equilibrium) potentials for both ions are identical. This requirement leads to the defining properties of the Donnan equilibrium, which applies simultaneously to two permeant ions. It is possible to build a model cell that reaches equilibrium and that has ICF, ECF, and membrane potential similar to that of real animal cells.

Real cells are permeable to sodium ions, however, and must expend metabolic energy, in the form of ATP, to "pump" sodium out against its concentration and electrical gradients. This pumping action allows the cell to maintain osmotic balance. Next, we will consider the effect of this sodium permeability on the electrical membrane potential. We will see that membrane potential depends not only on the concentrations of ions on the two sides of the membrane, as in the Nernst equation, but also on the relative permeability of the membrane to those ions.

MEMBRANE POTENTIAL: IONIC STEADY STATE

As we saw earlier in this chapter, two permeant ions can be at equilibrium across a cell membrane simultaneously. This Donnan equilibrium required that the membrane potential be equal to the Nernst potentials for the two ions. We also saw that real animal cells are permeable to sodium, so that three major ions—potassium, chloride, and sodium—can cross the plasma membrane. The remainder of this chapter will focus on the effect of sodium permeability on membrane potential and the quantitative relationship between ionic permeabilities and concentrations on the one hand and electrical membrane potential on the other.

Equilibrium potentials for sodium, potassium, and chloride

If the permeability of the cell membrane to sodium is not zero, then the resting membrane potential of the cell must receive a contribution from Na^+ as well as from K^+ and Cl^-, even though the sodium pump removes any sodium that leaks into the cell. This situation occurs for two reasons. First, electrical force per particle is much stronger than concentrational force per particle; therefore, even a tiny trickle of sodium that would cause a negligible change in internal concentration could produce large changes in membrane potential. Because the sodium pump responds only to changes in the bulk concentration of sodium inside the cell, it could not detect and respond to such tiny changes, even if they were accompanied by large changes in membrane potential. Second, although the sodium that leaks in is eventually pumped out, the efflux of sodium through the pump is coupled with an influx of potassium. Thus, a net transfer of positive charge into the cell is associated with sodium leakage.

Application of the Nernst equation to the concentrations of sodium, potassium, and chloride in the ICF and ECF of a typical mammalian cell (see Table 3.1) shows that the membrane potential cannot possibly achieve the equilibrium potentials of all three ions simultaneously. As we calculated earlier in this chapter, $E_K = E_{Cl} = \sim-80$ mV (actually a bit greater than −81 mV, given the values in Table 3.1). If $[Na^+]_o = 120$ mM and $[Na^+]_i = 12$ mM, then $E_{Na} = +58$ mV. The membrane potential, E_m, cannot simultaneously equal −80 mV and +58 mV. The actual value will fall somewhere between these two extremes. If the sodium permeability of the membrane were actually zero, E_m would be determined solely by E_K and E_{Cl} and would equal −80 mV. Conversely, if chloride and potassium permeability were zero, E_m would be determined only by sodium and would lie at E_{Na}, +58 mV. Because the permeabilities of all three ions are nonzero, a struggle will occur between Na^+, which tends to make $E_m = +58$ mV, and K^+ and Cl^-, which tend to make $E_m = -80$ mV.

Two factors determine where E_m will actually fall:

- Ion concentrations, which determine the equilibrium potentials for the ions.

- Relative ion permeabilities, which determine the relative importance of a particular ion in governing where E_m lies.

Before expressing these relations quantitatively, it will be useful to consider the mechanism of ionic permeability in more detail.

Ion channels in the plasma membrane

The permeability of a membrane to a particular ion is a measure of the ease with which that ion can cross the membrane. Recall that ions cannot cross membranes through the lipid portion of the membrane; they must cross through aqueous pores or channels in the membrane. Thus, the ionic permeability of a membrane is determined by the properties of the ion pores or channels in that membrane—that is, it is a property of the membrane itself. The total permeability of a membrane to a particular ion is governed by the total number of membrane channels that allow that ion to cross and by the ease with which the ion can pass through a single channel. Ion channels consist of protein molecules that are associated with the membrane, and thus an important function of membrane proteins involves the regulation of the cell membrane's ionic permeability. In later chapters, we will discuss how specialized channels modulate ionic permeability in response to chemical or electrical signals and the role of such changes in permeability in signal processing in the nervous system.

Not all membrane channels allow all ions to cross with equal ease. Some channels permit only cations to pass through, while others allow only anions to enter and exit. Some channels are even more selective, allowing K^+ through but not Na^+, or vice versa. Thus, a membrane can possess highly variable permeabilities for different ions, depending on the number of channels for each ion.

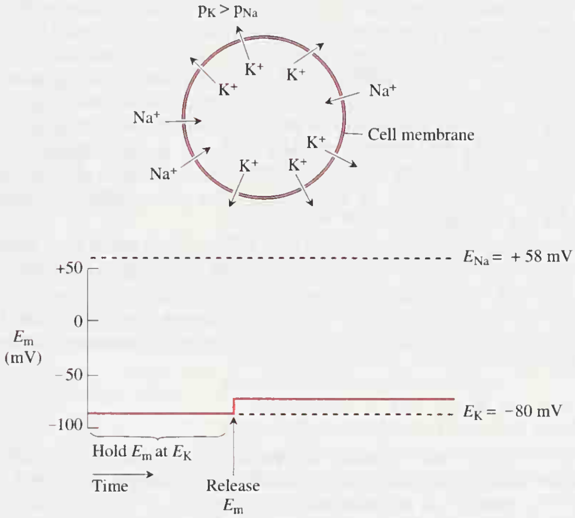
Membrane potential and ionic permeability

To see how the actual value of membrane potential depends on the relative permeabilities of the competing ions, consider the situation illustrated in Figure 4.7. This model cell is much more permeable to K^+ than to Na^+. In other words, many channels allow K^+ to cross the membrane but only a few permit Na^+ to cross. Initially we connect the cell to an apparatus that artificially maintains the resting membrane potential at E_K, so that $E_m = E_K = -80$ mV. (We could, for example, use a voltage clamp apparatus, as described in chapter 6.) What will happen to E_m when we switch off the apparatus and allow E_m to take on any value it wishes?

To determine the answer to this question, we must keep in mind one important principle: *If the membrane potential is not equal to the equilibrium potential for an ion, that ion will move across the membrane in such a way as to force* E_m *toward the equilibrium potential for that ion.* Figure 4.8 illustrates an example of how K^+ might move across a cell membrane in response to changes in E_m. In this case, a cell is connected to an apparatus that allows us to set the membrane potential. Initially, we set E_m to E_K. Recall that when $E_m = E_K$, the electrical force driving K^+ into the cell is balanced with the concentrational force driving K^+ out of the cell.

At time = *a*, we suddenly make the interior of the cell less negative, reducing the electrical potential across the cell membrane and decreasing the electrical force driving K^+ into the cell. Such a reduction in the electrical potential across the membrane is called a depolarization of the membrane. The electrical force will then be weaker than the oppositely directed concen-

Figure 4.7
The resting membrane potential of a cell that is more permeable to potassium than sodium. At the upward arrow, an apparatus that artificially maintains the membrane potential at E_K is abruptly switched off, and E_m is allowed to seek its own resting level.

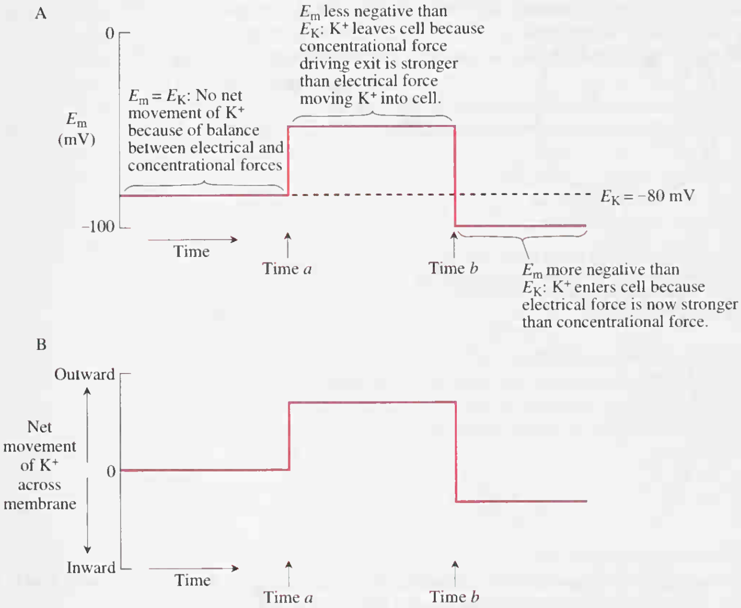


trational force, and a net movement of K^+ out of the cell will occur. This movement serves to move E_m back toward E_K—that is, it makes the interior of the cell more negative because of the efflux of positive charge.

At time = *b,* we suddenly make E_m more negative than E_K, hyperpolarizing the membrane. Now the electrical force will be stronger than the concentrational force and a net movement of K^+ into the cell will occur. This influx also moves E_m toward E_K, in this case by adding positive charge to the interior of the cell.

Returning to the example given in Figure 4.7, we would expect that Na^+, which has an equilibrium potential of +58 mV, will enter the cell, bringing with it a positive charge. When we switch off the apparatus, forcing E_m to remain at E_K, this influx of sodium ions will cause the membrane potential to become more positive (that is, to move toward E_{Na}). As E_m moves toward E_{Na}, however, it will no longer be equal to E_K. As a consequence, K^+ will move out of the cell in response to the resulting imbalance between the potassium concentrational force and electrical force. Thus, a struggle will occur between K^+ efflux, which forces E_m toward E_K, and Na^+ influx, which forces E_m toward

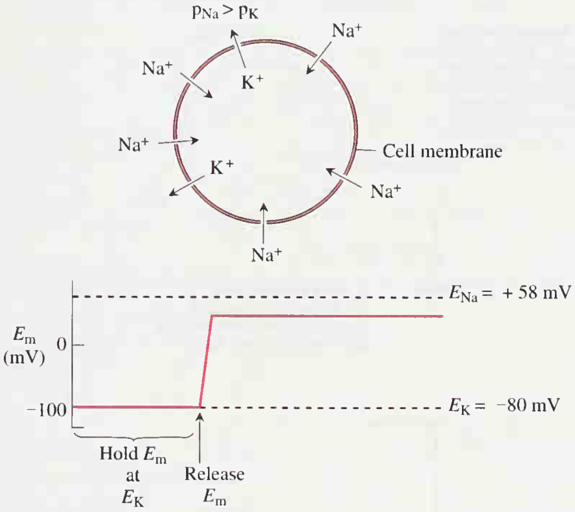
Figure 4.8
The effect of changes in membrane potential on the movement of potassium ions across the plasma membrane. When the membrane potential is artificially manipulated (A), potassium ions move across the membrane in a direction governed by the difference between E_m and E_K (B).



E_{Na}. Because K^+ permeability is much higher than Na^+ permeability, potassium ions can move out readily to counteract the electrical effect of the trickle of sodium ions into the cell. In this example, the balance between the movement of Na^+ into the cell and the exit of K^+ from the cell would be struck relatively close to E_K.

Figure 4.9 shows a different situation. In this case, the cell membrane's sodium permeability greatly exceeds its potassium permeability. That is, there are more channels for Na^+ than for K^+. Once again, we begin with $E_m = E_K = -80$ mV and then allow E_m to seek its own value. Sodium, with $E_{Na} = +58$ mV, enters the cell down its electrical and concentration gradients. The resulting accumulation of positive charge causes the cell to depolarize. In this case, however, potassium cannot move out as readily as sodium can enter the cell, and the influx of sodium will not be balanced as readily by

Figure 4.9
The resting membrane potential of a cell that is more permeable to sodium than potassium. An apparatus holding E_m at E_K is abruptly turned off at the upward arrow.



efflux of potassium. Thus, E_m will move farther from E_K and will reach a steady-state value closer to E_{Na} than to E_K.

The point of the last two examples is that the value of the membrane potential will be governed by the relative permeabilities of the permeant ions. *If a cell membrane is highly permeable to an ion, that ion can respond readily to deviations away from its equilibrium potential, and* E_m *will tend to be near that equilibrium potential.*

The Goldman equation

The examples discussed so far have focused on the qualitative relation between membrane potential and relative ionic permeabilities. The equation that gives the quantitative relation between E_m on the one hand and ion concentrations and permeabilities on the other is the **Goldman equation**, which is also called the **constant-field equation.** For a cell that is permeable to potassium, sodium, and chloride, the Goldman equation can be written as

$$E_m = \frac{RT}{F} \ln\left(\frac{p_K[K^+]_o + p_{Na}[Na^+]_o + p_{Cl}[Cl^-]_i}{p_K[K^+]_i + p_{Na}[Na^+]_i + p_{Cl}[Cl^-]_o}\right) \tag{4.6}$$

This equation is similar to the Nernst equation, except that it simultaneously takes into account the contributions of all permeant ions. (Appendix B contains information about the derivation of the Goldman equation.) Note that the concentration of each ion on the right side of the equation is scaled according to its permeability, p. Thus, if the cell is highly permeable to potassium, the potassium term on the right will dominate and E_m will approach the Nernst potential for potassium. If p_{Na} and p_{Cl} are zero, the Goldman equation will reduce to the Nernst equation for potassium, and E_m will exactly equal E_K, as we would expect if the only permeant ion were potassium.

Because it is easier to measure relative ion permeabilities than absolute permeabilities, the Goldman equation is often written in a slightly different form:

$$E_m = 58 \text{ mV} \log\left(\frac{[K^+]_o + b[Na^+]_o + c[Cl^-]_i}{[K^+]_i + b[Na^+]_i + c[Cl^-]_o}\right) \tag{4.7}$$

In this case, the permeabilities have been expressed relative to the permeability of the membrane to potassium. Thus, $b = p_{Na}/p_K$, and $c = p_{Cl}/p_K$. We have also evaluated RT/F at room temperature, converted from natural log to log, and expressed the result in millivolts.

For most nerve cells, the Goldman equation can be simplified even further, by dropping the chloride term on the right. This approximation is valid because the contribution of chloride to the resting membrane potential is insignificant in most nerve cells. In this case, the Goldman equation becomes

$$E_m = 58 \text{ mV} \log\left(\frac{[K^+]_o + b[Na^+]_o}{[K^+]_i + b[Na^+]_i}\right) \tag{4.8}$$

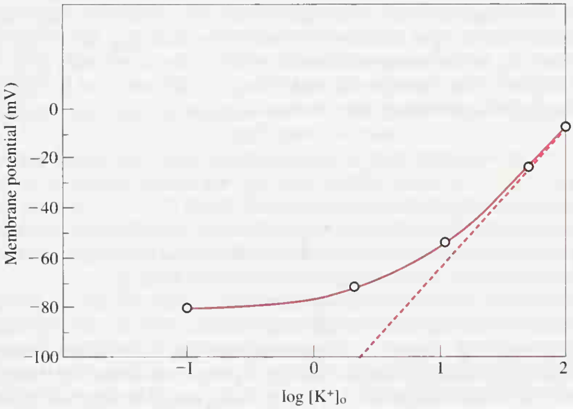
This form of the equation is most frequently encountered in neurophysiology. In nerve cells, the ratio of sodium to potassium permeability, b, is commonly approximately 0.02, although it may vary somewhat from one cell to another. That is, p_K is roughly 50 times higher than p_{Na}. According to Equation (4.8), E_m would be approximately -71 mV for a cell with $[K^+]_i$ = 125 mM, $[K^+]_o$ = 5 mM, $[Na^+]_i$ = 12 mM, $[Na^+]_o$ = 120 mM, and $b = 0.02$. What would E_m be for the same cell if b were 1.0 (that is, if $p_{Na} = p_K$) instead of 0.02?

The Goldman equation tells us quantitatively what we would expect qualitatively. If p_K is 50 times higher than p_{Na}, we would expect E_m to be nearer to E_K than to E_{Na}. Indeed, Equation (4.8) yields $E_m = -71$ mV, which is much nearer to E_K (-80 mV) than to E_{Na} ($+58$ mV). The difference between E_m and E_K reflects the steady-state influx of sodium ions carrying a positive charge into the cell and maintaining a depolarization from E_K.

The applicability of the Goldman equation to a real cell can be tested experimentally by varying the concentration of potassium in the ECF and measuring the resulting changes in membrane potential. If membrane potential were determined solely by the distribution of potassium ions across the cell membrane—that is, if b in Equation (4.8) were 0—E_m would be dictated by the potassium equilibrium potential. In this situation, a plot of measured membrane potential against log $[K^+]_o$ would yield a straight line with a slope of 58 mV per tenfold change in $[K^+]_o$. This straight line would be a plot of E_m as calculated from the Nernst equation for different values of external potassium concentration (the dashed line in Figure 4.10). The actual measured values of E_m of a nerve fiber observed at several external potassium concentrations fall along a line (the solid line in Figure 4.10) that differs from that expected from the Nernst equation. This line was drawn according to Equation (4.8). Thus, this experiment demonstrates that the real value of membrane potential in the nerve fiber is determined jointly by the potassium and sodium ions. Experiments of this type by Hodgkin and Katz in 1949 first demonstrated the role of sodium ions in the resting membrane potential of real cells.

Equation (4.8) is a reasonable approximation to Equation (4.7) only if p_{Cl}/p_K is negligible. To determine if it is valid to ignore the contribution of chloride—that is, to use Equation (4.8)—experiments can be performed in which the concentration of chloride in the ECF is varied rather than the concentration of potassium. When that was done on the type of nerve cell used in the experiment of Figure 4.10, a tenfold reduction of $[Cl^-]_o$ was found to cause only a 2 mV change in the resting membrane potential. Thus, for

Figure 4.10
The experimentally determined relationship between external potassium concentration and resting membrane potential of an axon in the spinal cord of the lamprey. The circles show the measured value of membrane potential at five different values of $[K^+]_o$. The dashed line gives the potassium equilibrium potential calculated from the Nernst equation. The solid line shows the prediction from the Goldman equation with internal and external sodium and potassium concentrations appropriate for the lamprey nervous system.



that type of cell (and other nerve cells), membrane potential is relatively unaffected by chloride concentration, and Equation (4.8) is valid. Because the membranes of other kinds of cells (such as muscle cells) have larger chloride permeability, their membrane potentials would be more strongly dependent on external chloride concentration. This has been demonstrated experimentally for muscle cells by Hodgkin and Horowicz.

Ionic steady state

The Goldman equation represents the actual situation seen in animal cells. The membrane potential of the cell takes on a steady-state value that reflects a fine balance between competing influences. Keep in mind, however, that neither sodium ions nor potassium ions are at equilibrium at that potential: sodium ions are continually leaking into the cell and potassium ions are continually leaking out. If this process continued, the concentration gradients for sodium and potassium would eventually run down and the membrane potential would decline to zero as the ionic gradients collapsed. The situation would resemble a flashlight that has been left on, with the batteries slowly discharging.

To prevent the intracellular accumulation of sodium and loss of potassium, the cell must expend energy to restore the ionic gradients. Here again is an important role for the sodium pump. Metabolic energy stored in ATP is used to expel the sodium that leaks in and to regain the potassium that was lost. In this way, the cell's "batteries" are recharged using metabolic energy. Viewed in this light, the steady-state membrane potential of a cell represents chemical energy that has been converted into a different form and stored in the ionic gradients across the cell membrane. In chapter 5, we will see how some cells—most notably the cells that make up the nervous system—tap this stored energy to generate signals that can carry information and allow animals to move and function in their environment.

The chloride pump

Because the resting membrane potential of a cell is not at either the sodium or potassium equilibrium potentials, there is a continuous net flux of sodium across the membrane. As we have just seen, metabolic energy must be expended to maintain the ionic gradients for sodium and potassium. What about chloride? Given the internal and external concentrations shown in Table 3.1, the equilibrium potential for chloride would be approximately -80 mV, but the resting membrane potential is about -71 mV. Thus, we would expect a steady-state influx of chloride into the cell as a result of this imbalance between the electrical and concentration gradients for chloride. Eventually, this influx would raise the internal chloride concentration until the new chloride equilibrium potential reached -71 mV, equal to the resting membrane potential. At that point, the concentration gradient for chloride would be reduced sufficiently to come into balance with the resting membrane potential. Using the Nernst equation, we can calculate that chloride would have to rise to 7.5 mM (from its usual 5 mM) to establish this new equilibrium state.

In some cells, this does indeed appear to happen: chloride reaches a new equilibrium governed by the resting membrane potential of the cell. (The cell also gains the same small amount of potassium; because so much potassium remains inside the cell, a change of a few millimolar in potassium concentration changes the potassium equilibrium potential very little, however.) In other cells, the chloride equilibrium potential continues to differ from the resting membrane potential, just as the sodium and potassium equilibrium potentials remain different from E_m. The only way this non-equilibrium condition can be maintained is by expending energy to keep the internal chloride constant—that is, there must be a chloride pump that is similar in function to the sodium–potassium pump. In most cells, the chloride pump moves chloride ions out of the cell, keeping the chloride equilibrium potential more negative than the resting membrane potential. In a few cases, however, an inwardly directed chloride pump has been discovered.

Less is known about the molecular machinery of the chloride pump than that of the sodium–potassium pump. It is thought to involve an ATPase in some instances, so that the energy released by hydrolysis of ATP serves as the immediate driving energy for the pumping. In other cases, the pump may use energy stored in gradients of other ions to drive chloride movement.

Electrical current and the movement of ions across membranes

An electrical current represents the movement of charge through space. In a wire like that carrying electricity in your house, the electrical current is a flow of electrons. In a solution of ions, a flow of current is carried by movement of ions. That is, the charges that move during an electrical current flow in a solution consist of the charges on the ions in solution. Thus, the movement of ions through space—such as from the outside of a cell to the inside of a cell—constitutes an electrical current, just as the movement of electrons through a wire constitutes an electrical current.

By envisioning ion flows as electrical currents, we can obtain a different perspective on the factors governing the steady-state membrane potential of cells. At the steady-state value of membrane potential, there is a steady influx of sodium ions into the cell and a steady efflux of potassium ions out of the cell. Thus, a steady electrical current, carried by sodium ions, flows across the cell membrane in one direction, and a second current, carried by potassium ions, flows across the membrane in the opposite direction. By convention, electrical current is assumed to flow from the plus to the minus terminal of a battery. Thus, we talk about currents in a wire as though the current is carried by positive charges. By extension, the sodium current is an *inward* membrane current (the transfer of positive charge from the outside to the inside of the membrane), and the potassium current is an *outward* membrane current.

As shown in our discussion of the Goldman equation, a steady-state value of membrane potential will be achieved when the influx of sodium is exactly balanced by the efflux of potassium. In electrical terms, the steady state is characterized by a sodium current, i_{Na}, that is equal and opposite to the potassium current i_K. In equation form, this relation can be written as

$$i_K + i_{Na} = 0 \tag{4.9}$$

Thus, at the steady state the net membrane current is zero. This makes electrical sense, if we keep in mind that the cell membrane can be treated as an electrical capacitor. If the sum of i_{Na} and i_K were not zero, a net flow of current would occur across the membrane. Thus, there would be a net movement of charge onto (or from) the membrane capacitor. Any such movement of charge would change the voltage across the capacitor (the membrane potential). (From the relation $q = CV$, if q changes and C remains constant, then V must necessarily change.) Equation (4.9), then, is a requirement of the steady-state condition; if the equation does not hold true, then the membrane potential cannot be at a steady-state level.

In cells in which an appreciable flow of chloride ions moves across the membrane, Equation (4.9) must be expanded to include the chloride current, i_{Cl}:

$$i_K + i_{Na} + i_{Cl} = 0 \tag{4.10}$$

Equation (4.10) is, in fact, the starting point in the derivation of the Goldman equation (see Appendix B). Because of the negative charge on chloride and the electrical convention for the direction of current flow, an outward movement of chloride ions is actually an inward membrane current.

Factors affecting ionic current across a cell membrane

What factors govern the amount of current carried across the membrane by a particular ion? One important factor is the difference between the equilibrium potential for the ion and the actual membrane potential. As an example, consider the movement of potassium ions across the membrane. If $E_m = E_K$, the electrical and concentrational forces for potassium are balanced and there is no net movement of potassium across the membrane. In this situation, $i_K = 0$. If $E_m \neq E_K$ (see Fig. 4.8), the resulting imbalance in electrical and concentrational forces will drive a net movement of potassium across the membrane. The larger the difference between E_m and E_K, the larger the imbalance between the electrical and concentration gradients and the larger the net movement of potassium. Thus, i_K depends on $E_m - E_K$. This difference is called the **driving force** for membrane current carried by an ion.

The permeability of the membrane to an ion is also an important determinant of the amount of membrane current carried by that ion. If the permeability is high, the ionic current at a particular value of driving force will be higher than if the permeability were low. Because p_K is much greater than p_{Na}, the potassium current resulting from a 10 mV difference between E_m and E_K will be much larger than the sodium current resulting from a 10 mV difference between E_m and E_{Na}. This relationship is, in electrical terms, the reason that the steady-state membrane potential of a cell lies closer to E_K than to E_{Na}: to satisfy Equation (4.9), the driving force for sodium entry ($E_m - E_{Na}$) must greatly exceed the driving force for potassium exit ($E_m - E_K$).

Membrane permeability versus membrane conductance

To place the discussion in the preceding section on more quantitative ground, we will introduce a new concept that is closely related to membrane permeability—**membrane conductance.** The conductance of a membrane to an ion provides an index of the ion's ability to carry current across the membrane. The higher the conductance, the greater the ionic current for a given driving force. Conductance is analogous to the reciprocal of the resistance of an electrical circuit to current flow. The higher the resistance of a circuit, the lower the amount of current that flows in response to a particular voltage. This behavior of electrical circuits can be conveniently summarized by Ohm's law: $i = V/R$. In this equation, i is the current flowing through a resistor, R, in the presence of a voltage gradient, V. Using potassium as an example, the equivalent form of the equation for the flow of an ionic current across a membrane is

$$i_{\mathrm{K}} = g_{\mathrm{K}}(E_{\mathrm{m}} - E_{\mathrm{K}}) \tag{4.11}$$

where g_{K} is the conductance of the membrane to potassium ions. The unit of electrical conductance is the Siemen, abbreviated S; a 1 V battery will drive 1 ampere of current through a 1 S conductance.

Similar equations can be written for sodium and chloride:

$$i_{\mathrm{Na}} = g_{\mathrm{Na}}(E_{\mathrm{m}} - E_{\mathrm{Na}}) \tag{4.12}$$

$$i_{\mathrm{Cl}} = g_{\mathrm{Cl}}(E_{\mathrm{m}} - E_{\mathrm{Cl}}) \tag{4.13}$$

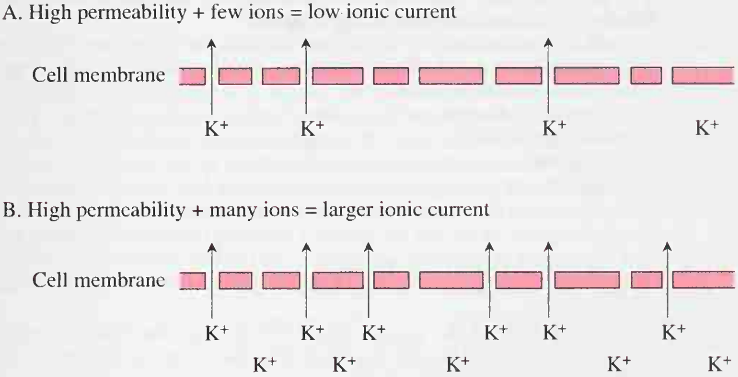
For the usual values of E_{m} (−71 mV), E_{K} (−80 mV), and E_{Na} (+58 mV), the potassium current is a positive number and the sodium current is a negative number, as required by the fact that the two currents flow in opposite directions across the membrane. By convention in neurophysiology, an outward membrane current (such as i_{K}, at the steady-state E_{m}) is positive and an inward current (such as i_{Na}, at the steady-state E_{m}) is negative.

Although the membrane conductance to an ion is closely related to the membrane permeability to that ion, the two are not identical. The membrane current carried by a particular ion, and hence the membrane conductance to that ion, is proportional to the rate at which ions cross the membrane (that is, the ionic flux). That rate depends not only on the membrane's permeability to the ion, but also on the number of available ions in the solution.

As an example, imagine a cell membrane containing many potassium channels (Fig. 4.11). The permeability of this membrane to potassium is, therefore, high. If the solution includes only a few potassium ions, however, a K^+ is unlikely to find a channel and cross the membrane. In this case, the potassium current will be low and the conductance of the membrane to K^+ will be low even though the permeability is high. On the other hand, if many potassium ions are available to cross the membrane (see Fig. 4.11B), a K^+ is much more likely to encounter a channel, and the corresponding rate of K^+ flow across the membrane will be high. The permeability remains fixed, but the ionic conductance increases when more potassium ions become available. In this way, the potassium conductance of the membrane depends on the concentration of potassium at the membrane.

For the most part, however, a change in a membrane's permeability to an ion produces a corresponding change in the membrane's conductance to that ion. Thus, when dealing with changes in membrane conductance—as in the

Figure 4.11
An illustration of the difference between permeability and conductance. (A) A cell membrane is highly permeable to potassium, but the solution contains very little potassium. Therefore, the ionic current carried by potassium ions is small and the membrane conductance to potassium is small. (B) The same cell membrane in the presence of higher potassium concentration has a larger potassium conductance because the potassium current is larger. The permeability, however, is the same as in A.



A. High permeability + few ions = low ionic current

B. High permeability + many ions = larger ionic current

next chapter—we can treat a conductance change as a direct index of the underlying permeability change.

Behavior of single ion channels

At this point, it is worthwhile considering the properties of the ionic current flowing through an individual ion channel. We have already seen that the total membrane permeability of a cell to a particular ion depends on the number of channels available to the ion. In addition, the total permeability depends on how readily ions go through a single channel. In Equations (4.11) through (4.13), we showed that the ionic current across a membrane is equal to the product of the electrical driving force and the membrane conductance. Similar considerations apply to the ionic current flowing through a single open ion channel. For a potassium channel, for example, we can write the following equation:

$$i_S = g_S(E_m - E_K) \tag{4.14}$$

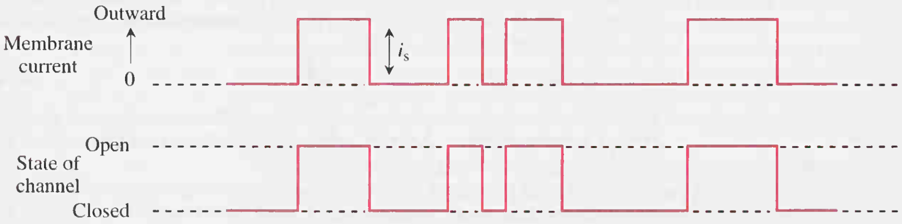
where i_S is the single-channel current and g_S is the single-channel conductance for the potassium channel. Analogous equations could be written for single sodium and chloride channels.

What would we expect if we could measure directly the electrical current flowing through a single ion channel in a cell membrane? To this point, we have treated ion channels as simple open pores that allow ions to cross the membrane. Real ion channels exhibit somewhat more complex behavior. The protein molecule that forms the channel can apparently exist in two conformational states: one in which the pore is open and ions are free to move through it, and one in which the pore is closed and ion movement is blocked. (Actually, channels frequently show more than two functional states; for our purposes, however, we can treat channels as being either open or closed.) Thus, channels behave as though access to the pore is controlled by a "gate" that can be open or closed; for this reason, we refer to the opening and closing of the channel as **channel gating.**

The electrical behavior of such a gated ion channel is illustrated in Figure 4.12, which shows the electrical current we would measure through a small patch of cell membrane containing a single potassium channel. When the channel is in a closed state, no current flows across the membrane patch because potassium ions have no path across the membrane. When the channel protein abruptly undergoes a transition to the open state, an outward current suddenly appears as potassium ions exit the cell through the open pore. When the channel returns to the closed state, the current abruptly disappears again. As we will see later, the control of ion channel gating, and thus the control of the ionic conductance of the cell membrane, represents an important strategy for passing biological signals both within a cell and between cells.

The amplitude of the current that flows through the open channel is given by Equation (4.14), with the single-channel current depending on the electrical driving force and on the single-channel conductance. How large is the single-channel current in reality? It depends on the type of ion channel in question, because considerable variation in single-channel conductance is found among the various kinds of channels encountered in a cell membrane (all channels of a particular kind would have the same

Figure 4.12
The electrical current flowing through a single potassium channel. The bottom trace shows the state of the channel (either open or closed), and the top trace shows the resulting ionic current through the channel. At the beginning of the trace, the channel is closed, and no ionic current flows. When the channel opens, potassium ions begin to exit the cell through the channel, carrying an outward membrane current. The magnitude of the current (i_s) is given by Equation (4.14).



single-channel conductance, however). A value of approximately 20 pS might be considered typical (pS is the abbreviation for picoSiemen, or 10^{-12} Siemen). If the conductance is 20 pS and the driving force is 50 mV, then Equation (4.9) indicates that the single-channel current would be 10^{-12} A (or 1 pA, which corresponds to roughly 6 million monovalent ions per second). A small current indeed!

Using a measurement technique called the patch clamp, it has proved possible to measure directly the electrical current flowing through a single open ion channel. This technique, invented by Erwin Neher and Bert Sakmann, will be discussed in more detail in chapter 7. The ability to make such measurements from single channels has revolutionized the study of ion channels and made possible much of our knowledge about how channels work.

What is the relationship between the total conductance of the cell membrane to an ion [Equations (4.11) through (4.13)] and the single-channel conductance? If, for example, a cell includes only one class of potassium channel with single-channel conductance of g_S, then the total membrane conductance to potassium, g_K, would be given by

$$g_K = N g_S P_o \tag{4.15}$$

where N is the number of potassium channels in the entire cell membrane and P_o is the average proportion of time that an individual channel remains in the open state. If the individual channels are always closed, then both P_o and g_K would be zero. Conversely, if individual channels are always open, then P_o is 1 and g_K will be the sum of all individual single-channel conductances (i.e., $N \times g_S$).

SUMMARY OF IONIC STEADY STATE

In real cells, the resting membrane potential is the point at which sodium influx is exactly balanced by potassium efflux. This point depends on the relative membrane permeabilities to sodium and potassium; in most cells, p_K is much higher than p_{Na} and the balance is struck close to E_K. The Goldman equation gives the quantitative expression of the relation between membrane potential and ion concentrations and permeabilities.

Because the steady-state membrane potential lies between the equilibrium potentials for sodium and potassium, a constant exchange of intracellular potassium for sodium occurs. This process would lead to progressive decline of the ionic gradients across the membrane if not for the action of the sodium–potassium pump. Metabolic energy, in the form of ATP used by the pump, provides for the long-term maintenance of the sodium and potassium gradients.

In the absence of a chloride pump, the chloride equilibrium potential changes to accommodate the value of the membrane potential established by sodium and potassium. In some cells, however, a chloride pump maintains the internal chloride concentration in a non-equilibrium state, just as the sodium–potassium pump maintains internal sodium and potassium concentrations at non-equilibrium values.

The steady-state fluxes of potassium and sodium ions constitute electrical currents across the cell membrane. At the steady-state E_m, these currents cancel one another so that the net membrane current is zero. The membrane current carried by a particular ion is given by an ionic form of Ohm's law—that is, by the product of the driving force for that ion and the membrane conductance to that ion. The driving force consists of the difference between the actual value of membrane potential and the equilibrium potential for that ion. Conductance is a measure of the ion's ability to carry electrical current across the membrane, and is closely related to the membrane permeability to the ion.

Individual ion channels behave as though access to the pore through which ions can cross the membrane is controlled by a gate. When the gate is open, the channel conducts and electrical current flows across the membrane; when it is closed, no current flow occurs. The current through a single open channel is given by the ionic form of Ohm's law—that is, the driving force multiplied by the single-channel conductance.

5

Generation of Nerve Action Potential

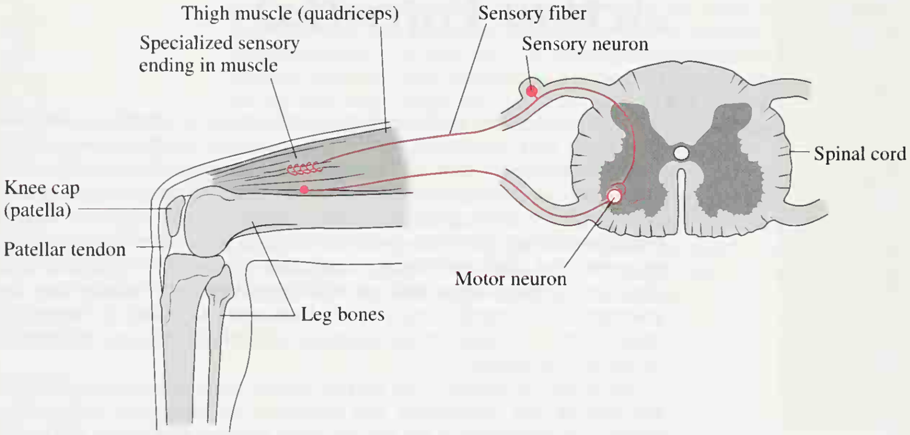
In chapters 3 and 4, we focused on general aspects of electrical membrane potential that are shared by all cells. Each cell must achieve osmotic balance, all cells possess a differential distribution of ions across the membrane, and all cells obey electrochemical principles in maintaining that transmembrane ionic gradient. In this chapter, we will begin to consider properties that are specific to particular kinds of cells: those that are capable of modulating their membrane potential in response to stimulation from their environment. These cells are called **excitable cells** because they can generate active electrical responses that can serve as signals or triggers for other events. The most notable examples of excitable cells are the neurons of the nervous system.

As we saw in chapter 1, the nervous system must receive input, transmit and analyze that information, and coordinate an appropriate action in response. Our discussion of the patellar reflex revealed that one of the fundamental signals used to carry such information is the **action potential**, the long-distance signal carried along the axons of the sensory and motor neurons in the patellar reflex. In this chapter, we will turn our attention to the mechanisms underlying the action potential, its origin, and its propagation throughout a neuron. We will find that simple modifications of the scheme for the origin of the membrane potential presented in chapter 3 can explain how neurons carry out the vital signaling functions performed by the nervous system.

To set the stage for our discussion of the generation and transmission of signals in the nervous system, we will return to the patellar reflex, the knee-jerk reflex that was described in chapter 1. Recall that this reflex is elicited by a sudden stretching of the quadriceps muscle at the front of the thigh. A sharp blow to the patellar tendon pulls the knee cap down and stretches the quadriceps muscle, which activates sensory neurons with endings in the muscle (Fig. 5.1). The message that the muscle has been stretched travels from the muscle along the axons of the sensory neurons, which course through the nerve innervating the muscle and terminate in the lower spinal cord. Activity in the sensory neurons is then passed to other neurons in the spinal cord, including the motor neurons that send axons back through the same nerve to the thigh to make contact with the quadriceps muscle. Activity in the motor neurons causes the muscle to contract.

Neurons are structurally complex cells, with long fibrous extensions that are specialized to receive and transmit information throughout the nervous system. This complexity can be appreciated by examining the delicate structure of a motor neuron, which is shown schematically in Figure 5.2A. The cell

Figure 5.1
A schematic representation of the patellar reflex. The sensory neuron is activated by stretching the thigh muscle and subsequently activates motor neurons in the spinal cord. Activity in the motor neuron causes the thigh muscle to contract.



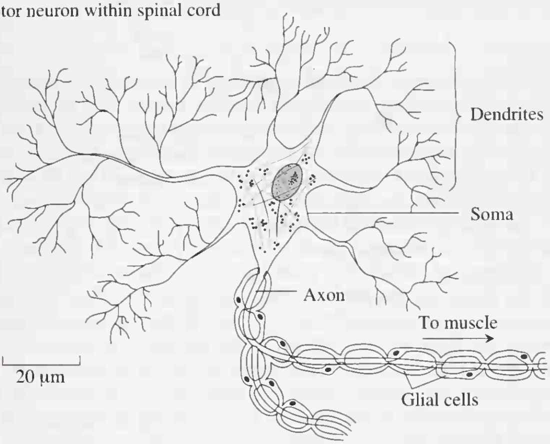
body, or **soma**, of the motor neuron—where the nucleus resides—constitutes only a small part of the cell. In the case of motor neurons involved in the patellar reflex, the soma is typically only 20 to 30 μm in diameter. The soma gives rise to a tangle of profusely branching processes called **dendrites**, which might spread out for several millimeters within the spinal cord. The dendrites are specialized to receive signals passed along by other neurons, such as the sensory neurons of the patellar reflex, and to funnel those signals to the soma. The soma also gives rise to a thin fiber, the **axon**, that is specialized to transmit activity from the neuron to other neurons or, in the case of the motor neuron, to the cells of the muscles. In some neurons, the axon may also branch profusely and carry signals to many parts of the nervous system.

As shown in Figure 5.2B, the sensory neuron of the patellar reflex is structurally much simpler than the motor neuron. Its soma, which is located just outside the spinal cord in the **dorsal root ganglion**, gives rise to only a single process. This process bifurcates to form the axon that carries the signal generated by stretch from the muscle into the spinal cord.

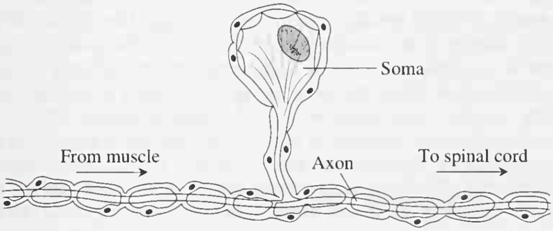
In this chapter, we will provide a descriptive introduction to the action potential and its mechanism; the next chapter presents in more advanced form the elegant physiological experiments that elucidated this mechanism. In later chapters of this part of the book, we will discuss how the activity is transmitted from the sensory neuron to the motor neuron and how the muscle contracts in response to the activity of the motor neuron.

Figure 5.2
Structures of single neurons involved in the patellar reflex. (A) A motor neuron within the spinal cord. (B) A sensory neuron just outside the spinal cord.

A
Motor neuron within spinal cord



B
Sensory neuron just outside spinal cord



THE ACTION POTENTIAL

Ion permeability and membrane potential

In chapter 4, we saw that membrane potential is governed by the relative permeabilities of the permeant ions. If the sodium permeability of a cell exceeds its potassium permeability, the membrane potential will be closer to

E_{Na} than to E_K. Conversely, if a cell has greater potassium permeability than sodium permeability, E_m will lie closer to E_K.

In all cases discussed so far, ionic permeability has been treated as a fixed characteristic of the cell membrane. The ionic permeability of the plasma membrane of excitable cells, however, can vary. Specifically, we will see that a transient, dramatic increase in sodium permeability underlies the generation of the nervous system's basic signal, the action potential.

Measuring the long-distance signal in neurons

What kind of signal carries the message along the sensory neurons in the patellar reflex? As mentioned earlier, the nervous system uses electrical signals, which can be monitored by measuring changes in the electrical potential associated with the activation of the reflex. This measurement can be carried out by placing an ultrafine probe inside the sensory axon to measure the electrical membrane potential of the neuron. A voltmeter is connected to measure the voltage difference between point *a,* at the tip of the ultrafine probe, and point *b,* a reference point in the ECF. Figure 5.3 illustrates the recording arrangement. When the probe is outside the sensory axon (Fig. 5.3B), both the probe and the reference point lie in the ECF, and the voltmeter records no voltage difference. When the probe is inserted into the sensory fiber, however, we measure the voltage difference between the inside and outside of the neuron, the membrane potential. In neurophysiology, this process of measuring the transmembrane voltage of a cell is called intracellular recording, and the ultrafine probe is called an intracellular electrode. As expected from the discussion in chapter 4, the membrane potential of the sensory fiber is approximately −70 mV.

When the muscle is stretched (see Fig. 5.3B), a dramatic change is noted in the membrane potential measured in the sensory fiber. After a small delay, a sudden jump occurs in membrane potential in which the potential transiently moves in a positive direction (a depolarization) and actually reverses its sign for a brief period. When the potential returns toward its resting value, it may briefly become more negative than its normal resting value. The transient jump in potential is called an action potential, and it represents the long-distance signal of the nervous system. If the stretch is sufficiently strong, it might elicit a series of action potentials, each with the same shape and amplitude. Figure 5.3C shows actual examples of a series of action

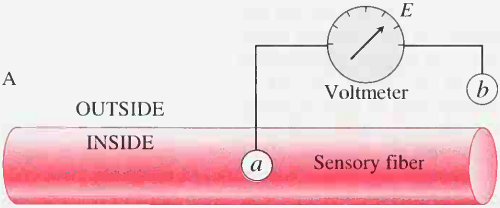
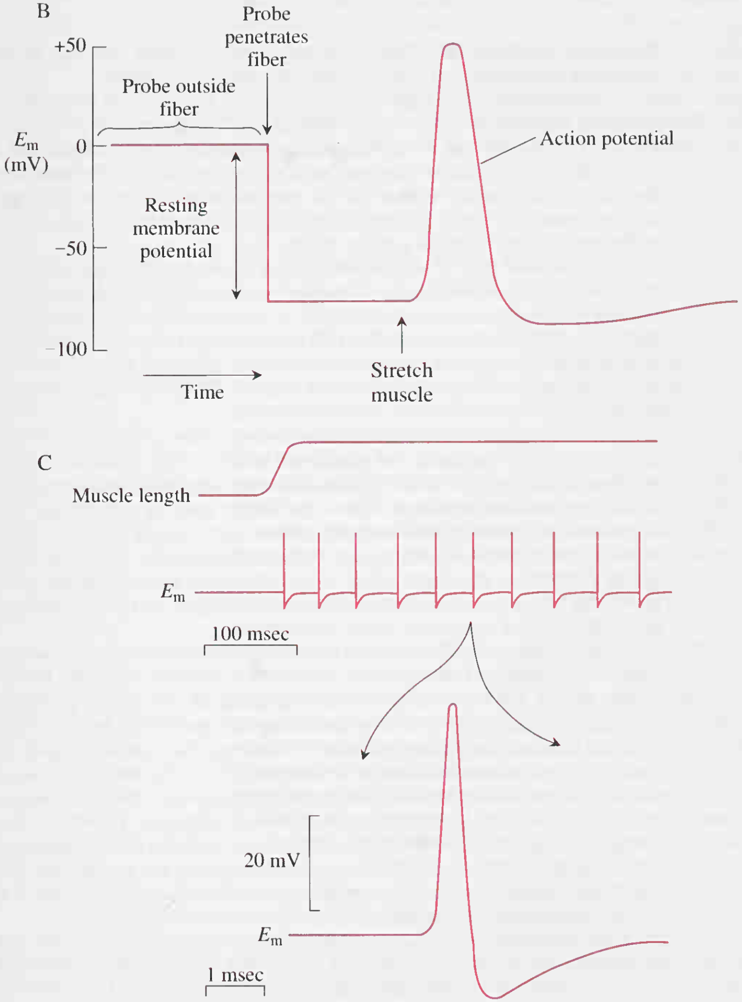


Figure 5.3
An example of an action potential in a neuron. (A) An experimental arrangement for recording the membrane potential of a nerve cell fiber.

Figure 5.3 (continued)

(B) Resting membrane potential and an action potential recorded via a voltage-sensing probe inside the sensory neuron of the patellar reflex loop. (C) Actual intracellular recordings from a single stretch-receptor sensory fiber during the stretch of the muscle. The lower trace shows a single action potential on an expanded time scale to show its waveform in more detail.



(C) Unpublished data provided by L. M. Mendell, R. Rose, and M. Sedivec of the State University of New York at Stony Brook.

potentials recorded via an intracellular electrode inside a sensory axon during the stretching of a muscle.

Characteristics of the action potential

The action potential has several important characteristics that can be explained in terms of the underlying ionic permeability changes:

1. Action potentials are triggered by depolarization. The stimulus that initiates an action potential in a neuron is a reduction in the membrane potential—that is, a depolarization of the membrane. Normally, the depolarization is produced by some external stimulus, such as the stretching of the muscle in the case of the sensory neuron in the patellar reflex, or by the action of another neuron, as in the transmission of excitation from the sensory neuron to the motor neuron in the patellar reflex.

2. A threshold level of depolarization must be reached to trigger an action potential. A small depolarization from the normal resting membrane potential will not produce an action potential. In most neurons, it is necessary to depolarize the membrane by 10 to 20 mV to trigger an action potential; therefore, if a neuron has a resting membrane potential of −70 mV, the membrane potential must be reduced to −60 to −50 mV to trigger an action potential.

3. Action potentials are "all or nothing" events. Once a stimulus is strong enough to reach threshold, the amplitude of the action potential is independent of the strength of the stimulus. Thus, the amplitude and form of the action potential remain fixed. The event either goes to completion (if a depolarization is above the threshold) or does not occur at all (if the depolarization falls below the threshold). In this manner, the triggering of an action potential is like the firing of a gun: the speed with which the bullet leaves the barrel is independent of whether the trigger was pulled softly or forcefully.

4. An action potential propagates without decrement throughout a neuron, albeit at a speed much slower than the rate at which electricity propagates through a wire. Figure 5.3 shows intracellular recordings of the action potentials triggered in a sensory neuron by stretching the quadriceps muscle. If we recorded simultaneously from the sensory fiber near the muscle and near the spinal cord, we would find that the action potential at the two locations has the same amplitude and form. Thus, as the signal travels from the muscle to the spinal cord, its amplitude would remain unchanged. However, there would be a significant delay of almost 0.1 second between the occurrence of the action potential near the muscle and its arrival at the spinal cord. The conduction speed in a typical mammalian nerve fiber is approximately 10 to 20 m/s, although speeds as high as 100 m/s have been observed.

5. At the peak of the action potential, the membrane potential reverses sign, becoming inside positive. As shown in Figure 5.3, the membrane potential during an action potential transiently overshoots zero, so that the inside of the cell becomes positive with respect to the ECF for a brief time. This event is called the overshoot of the action potential. When the action potential repolarizes toward the normal resting membrane potential, it transiently becomes more negative than normal. This event is called the undershoot of the action potential.

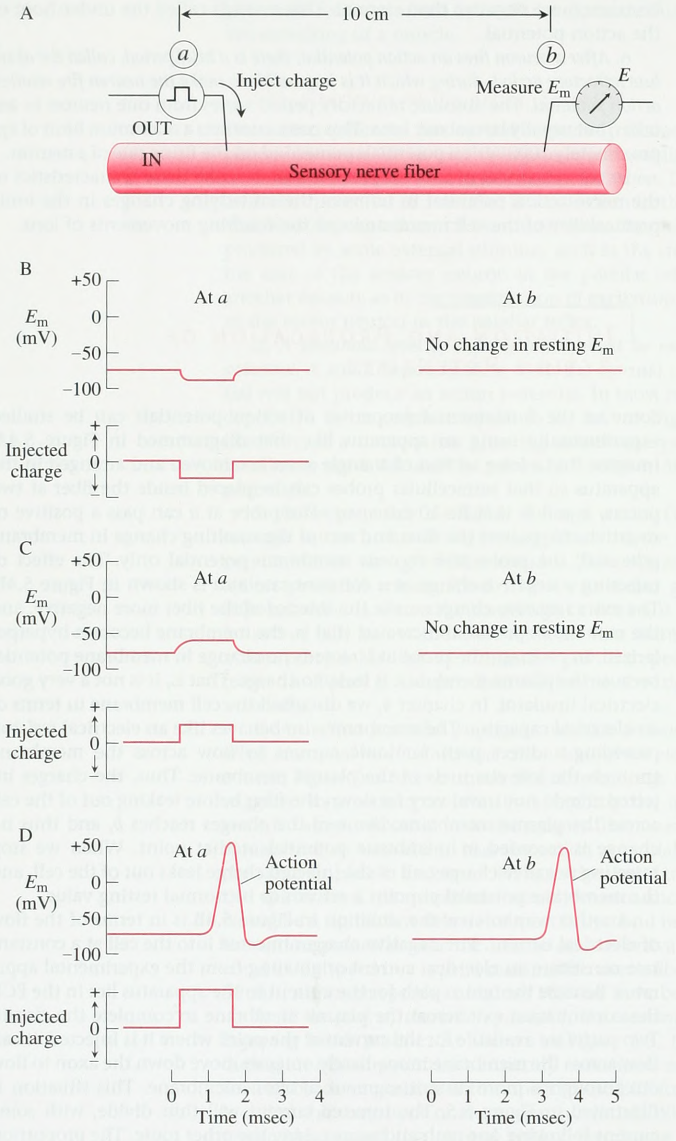
6. *After a neuron fires an action potential, there is a brief period, called the absolute refractory period, during which it is impossible to make the neuron fire another action potential.* The absolute refractory period varies from one neuron to another, but usually lasts about 1 ms. This constraint sets a maximum limit of approximately 1000 action potentials per second on the firing rate of a neuron.

In the remainder of this chapter, we will describe these characteristics of the nerve action potential in terms of the underlying changes in the ionic permeability of the cell membrane and the resulting movements of ions.

INITIATION AND PROPAGATION OF ACTION POTENTIALS

Some of the fundamental properties of action potentials can be studied experimentally using an apparatus like that diagrammed in Figure 5.4A. Imagine that a long section of a single axon is removed and arranged in the apparatus so that intracellular probes can be placed inside the fiber at two points, *a* and *b*, that lie 10 cm apart. The probe at *a* can pass a positive or negative charge into the fiber and record the resulting change in membrane potential; the probe at *b* records membrane potential only. The effect of injecting a negative charge at a constant rate at *a* is shown in Figure 5.4B. The extra negative charges make the interior of the fiber more negative, and the membrane potential increases; that is, the membrane becomes hyperpolarized. In contrast, the probe at *b* records no change in membrane potential because the plasma membrane is leaky to charge. That is, it is not a very good electrical insulator. In chapter 4, we discussed the cell membrane in terms of an electrical capacitor. The membrane also behaves like an electrical resistor, providing a direct path for ionic current to flow across the membrane through the ion channels of the plasma membrane. Thus, the charges injected at *a* do not travel very far down the fiber before leaking out of the cell across the plasma membrane. None of the charges reaches *b*, and thus no change is recorded in membrane potential at that point. When we stop injecting negative charges, all of the injected charge leaks out of the cell, and the membrane potential at point *a* returns to its normal resting value.

Another way to view the situation in Figure 5.4B is in terms of the flow of electrical current. The negative charges injected into the cell at a constant rate constitute an electrical current originating from the experimental apparatus. Because the return path for the current to the apparatus lies in the ECF, the current must exit across the plasma membrane to complete the circuit. Two paths are available for the current at the point where it is injected: it can flow across the membrane immediately or it can move down the axon to flow out through a more distant segment of axon membrane. This situation is illustrated in Figure 5.5. The injected current will thus divide, with some current following one path and some taking the other route. The proportion


A
10 cm
a
b
Inject charge
Measure E_m
E
OUT
IN
Sensory nerve fiber
B
+50
0
−50
−100
E_m (mV)
At *a*
At *b*
No change in resting E_m
Injected charge
+
0
C
At *a*
At *b*
No change in resting E_m
D
At *a*
At *b*
Action potential
Action potential
0
1
2
3
4
5
Time (msec)
Time (msec)

of current taking each path depends on the relative resistances of the two paths: more current will flow down the path with less resistance.

With each increment in distance along the axon, that fraction of the injected current that flowed down the axon again faces two paths. It can continue down the interior of the axon or it can cross the membrane at that point. The current will again divide, with a fraction exiting across the membrane and the remainder continuing down the nerve fiber. This process continues until all injected current has crossed the membrane, and no current remains to flow further down the interior of the axon. At that point, the injected current will not influence the membrane potential because no injected current will remain. Thus, the change in membrane potential produced by current injection (see Fig. 5.4A) decays with distance from the injection site. The greatest effect occurs at the injection site, and progressively less effect is recorded as injected current is lost across the plasma membrane. The cell membrane is not a particularly good insulator (it offers a low resistance to current flow compared, for example, with the insulator surrounding the electrical wires in your house), and the ICF inside the axon is not an especially effective conductor (its resistance to current flow is high compared with that of a copper wire). This set of circumstances favors the rapid decay of injected current with distance. In real axons, the hyperpolarization produced by current injected at a point decays by approximately 95% within 1 to 2 mm of the injection site.

Consider once again the experiment shown in Figure 5.4—in this case, the injection of positive charges into the axon (see Fig. 5.4C). If the number of positive charges injected is small, the effect on membrane potential is simply the reverse of the effect seen with injection of negative charges. That is, the membrane depolarizes while the charges are injected, but the effect does not reach *b*. When charge injection ceases, the extra positive charges leak out of the fiber, and membrane potential returns to normal. If the rate of injection of positive charge is increased (see Fig. 5.4D), the depolarization is larger. If the depolarization is sufficiently large, an all-or-nothing action potential, like that recorded when the muscle was stretched (see Fig. 5.3), is triggered at *a*. Once an action potential is triggered, the probe at *b* records a replica of the action potential at *a*, except that a time delay separates the occurrence of the action potential at *a* and its arrival at *b*.

These experiments show that action potentials are triggered by depolarization, not by hyperpolarization (characteristic 1 in the list given earlier), the depolarization must be large enough to exceed a threshold value (charac-

Figure 5.4

The generation and propagation of an action potential in a segment of a nerve fiber. (A) Apparatus for recording electrical activity of a segment of a sensory nerve fiber. The probes at points *a* and *b* allow recording of the membrane potential, and the probe at *a* also permits injection of charges into the fiber. (B) Injecting negative charges at *a* causes hyperpolarization at *a*. All injected charges leak out across the membrane before reaching *b*, and no change in membrane potential at *b* is recorded. (C) Injection of a small amount of positive charge produces a depolarization at *a* that does not reach *b*. (D) If a stronger depolarization is induced at *a*, it generates an action potential. The action potential propagates without decrement along the fiber and is recorded at full amplitude at *b*.

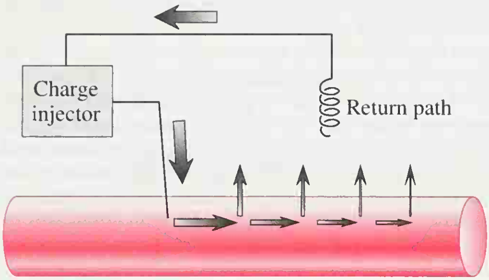


Figure 5.5
A schematic representation of the decay of injected current in an axon with distance from the site of current injection.

teristic 2), and the action potential travels without decrement throughout the nerve fiber (characteristic 4). What ionic properties of the neuron membrane can explain these properties?

CHANGES IN RELATIVE SODIUM PERMEABILITY DURING AN ACTION POTENTIAL

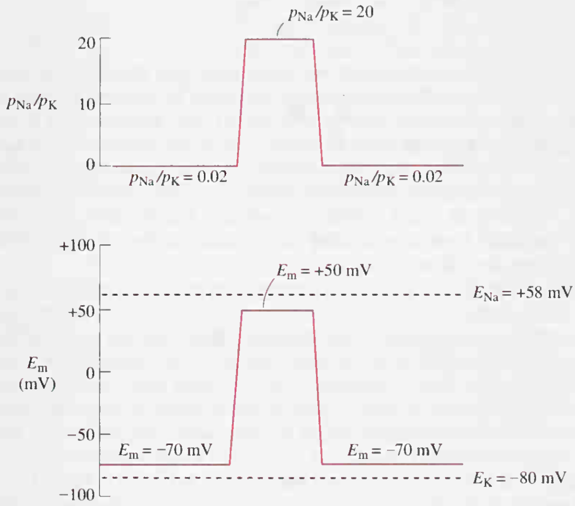
The key to understanding the origin of the action potential lies in our earlier discussion (in chapter 4) of the factors that influence the steady-state membrane potential of a cell. Recall that the resting E_m for a neuron will lie somewhere between E_K and E_{Na}. According to the Goldman equation, the exact point will be determined by the ratio p_{Na}/p_K. As we saw in chapter 4, p_{Na}/p_K of a resting neuron is approximately 0.02, and E_m is close to E_K.

What would happen to E_m if sodium permeability suddenly increased dramatically? In the example diagrammed in Figure 5.6, p_{Na} undergoes an abrupt thousandfold increase, so that $p_{Na}/p_K = 20$ instead of 0.02. According to the Goldman equation, E_m would then swing from −70 mV to +50 mV, near E_{Na}. When p_{Na}/p_K returns to 0.02, E_m will move back to its usual value near E_K. Note that the swing in membrane potential in Figure 5.6 reproduces qualitatively the change in voltage during an action potential. Indeed, such a transient increase in sodium permeability is responsible for the swing in membrane voltage from near E_K to near E_{Na}, and then back again, during an action potential.

Voltage-dependent sodium channels of the neuron membrane

Recall that ions must cross the membrane through transmembrane pores or channels. A dramatic increase in sodium permeability like that illustrated in Figure 5.6 requires a dramatic increase in the number of membrane channels through which sodium ions can enter the cell. Thus, the resting p_{Na} of the membrane of an excitable cell is only a small fraction of what it could be because most membrane sodium channels remain closed at rest. What stimulus causes these hidden channels to open and produces the positive swing of

Figure 5.6
The relationship between relative sodium permeability and membrane potential. When the ratio of sodium to potassium permeability (upper trace) changes, the position of E_m relative to E_K and E_{Na} is altered accordingly.



E_m during an action potential? The conducting state of sodium channels of excitable cells depends on membrane potential. When E_m is at the usual resting level or more negative, the sodium channels are closed. In the closed state, Na^+ cannot flow through them, and p_{Na} is low. When the membrane is depolarized, however, the channels open. The stimulus for opening of the voltage-dependent sodium channels of excitable cells is a reduction of the membrane potential.

Because the voltage-dependent sodium channels respond to depolarization, the response of the membrane to depolarization is regenerative, or explosive (Fig. 5.7). When the membrane is depolarized, p_{Na} increases and sodium ions carry positive charge into the cell. This influx of positive charge depolarizes the cell further, which increases p_{Na} still more and leads to greater depolarization. Such a process is inherently explosive and tends to continue until all sodium channels are open and the membrane potential has been driven near E_{Na}. Consequently, the nerve action potential displays its all-or-nothing behavior—once triggered, the process tends to run to completion.

Why should there be a threshold level of depolarization for triggering an action potential? Under the scheme discussed here, it might seem that any small depolarization would set the action potential off. In considering the

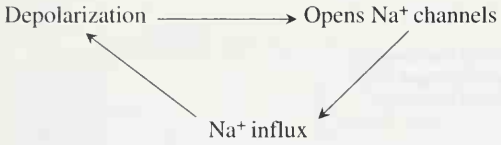


Figure 5.7
The explosive cycle leading to the depolarizing phase of an action potential.

effect of a depolarization, however, we must take into account the total current that flows across the membrane in response to the depolarization, not just the current carried by sodium ions. Recall that, at the resting E_m, p_K is much higher than p_{Na}; therefore, flow of K^+ out of the cell can counteract the influx of Na^+ even if depolarization brings a modest increase in p_{Na}. Thus, for a moderate depolarization, the efflux of potassium will exceed the influx of sodium, resulting in a net outward membrane current that keeps the membrane potential from depolarizing further and prevents the explosive cycle underlying the action potential.

To initiate the explosive process and generate an action potential, a depolarization must produce a net inward membrane current, which will in turn produce a further depolarization. A depolarization that produces an action potential must be sufficiently large to open numerous sodium channels and thereby overcome the efflux of potassium ions resulting from the depolarization. The **threshold potential** will be reached at that value of E_m where the influx of Na^+ exactly balances the efflux of K^+; any further depolarization will allow Na^+ influx to dominate, producing an explosive action potential.

One factor that influences the actual value of the threshold potential for a particular neuron is the density of voltage-sensitive sodium channels in the plasma membrane. If voltage-sensitive sodium channels are densely packed in the membrane, opening only a small fraction of them will produce a sizable inward sodium current. As a consequence, we would expect that the threshold depolarization would be smaller than if the channels were sparse. Often, the density of voltage-sensitive sodium channels is highest just at the point where a neuron's axon leaves the cell body (called the **initial segment**); that portion of the cell has the lowest threshold for action potential generation.

Another important factor in determining the threshold is the strength of the connection between depolarization and sodium channel opening. In some cases, the sodium channels have "hair triggers," and only a small depolarization from the resting E_m is required to open large numbers of channels. We would then expect the threshold to be close to the resting membrane potential. In other neurons, larger depolarizations are necessary to open appreciable numbers of sodium channels, and the threshold is further from resting E_m.

Repolarization

What causes E_m to return to rest again following the regenerative depolarization during an action potential? There are two important factors:

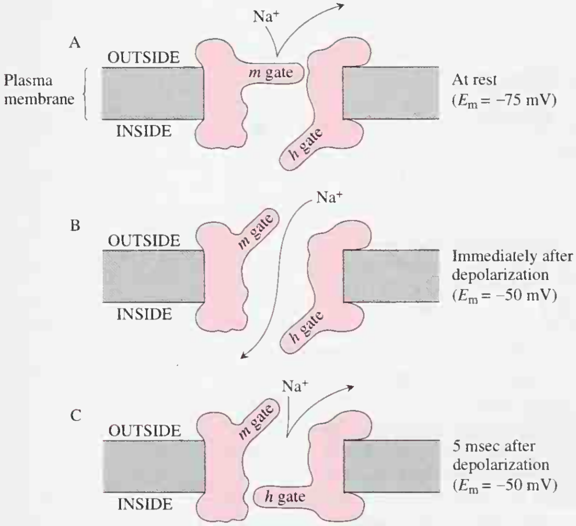
- The depolarization-induced increase in p_{Na} is transient.
- A delayed, voltage-dependent increase occurs in p_K.

The effect of depolarization on the voltage-dependent sodium channels is twofold. These effects are summarized in the diagram in Figure 5.8, which illustrates the behavior of a single voltage-sensitive sodium channel in response to a depolarization. The channel acts as though the flow of Na^+ is controlled by two independent gates. One gate, called the **m gate**, remains closed when E_m is equal to or more negative than the usual resting potential. This gate prevents Na^+ from entering the channel at the resting potential. The other gate, called the **h gate**, is open at the usual resting E_m. Both gates respond to depolarization, but with different speeds and in opposite directions. The m gate opens rapidly in response to depolarization; the h gate closes in response to depolarization, albeit slowly.

Immediately after a depolarization, the m gate is open, allowing Na^+ to enter the cell, but the h gate has not yet responded to the depolarization and remains open. One or two milliseconds later, the m gate is still open, but the

Figure 5.8

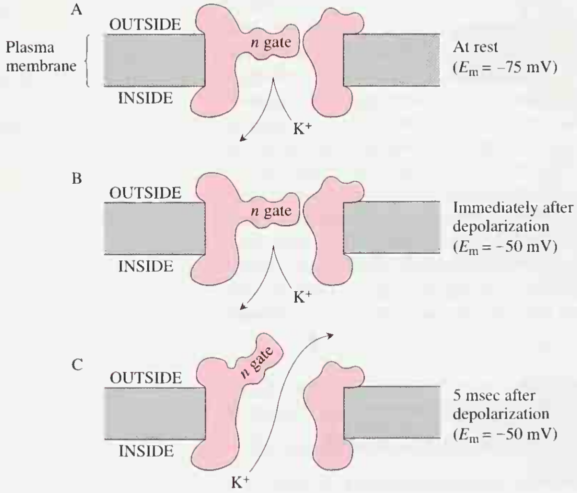
A schematic representation of the behavior of a single voltage-sensitive sodium channel in the plasma membrane of a neuron. (A) The state of the channel at the normal resting membrane potential. (B) Upon depolarization, the m gate opens rapidly and sodium ions are free to move through the channel. (C) After a brief delay, the h gate closes, returning the channel to a nonconducting state.



h gate has closed; as a result, the channel is again closed. Thus, p_{Na} first increases in response to a depolarization, then declines again even if the depolarization were maintained in some way. This delayed decline in sodium permeability upon depolarization is called **sodium channel inactivation.** This return of p_{Na} to its resting level would by itself be sufficient to bring E_m back to rest (see Fig. 5.6).

In addition to the voltage-sensitive sodium channels, voltage-sensitive potassium channels are found in the membranes of excitable cells. These channels also remain closed at the normal resting membrane potential. Like the sodium channel m gates, the gates on the potassium channels open upon depolarization, allowing the channel to conduct K^+ when the membrane potential becomes more positive. The gates of these potassium channels, which are called **n gates**, respond slowly to depolarization, so that p_K increases with a delay following a depolarization. This gating behavior of the voltage-sensitive potassium channels is summarized in Figure 5.9. Unlike the sodium channel, the potassium channel has no second gate that closes upon

Figure 5.9
The behavior of a single voltage-sensitive potassium channel in the plasma membrane of a neuron. (A) At the normal resting membrane potential, the channel remains closed. (B) Immediately after a depolarization, the channel remains closed. (C) After a delay, the n gate opens, allowing potassium ions to cross the membrane through the channel. The channel remains open as long as depolarization is maintained.



depolarization. Instead, the channel remains open as long as the depolarization is maintained and closes only when membrane potential returns to its normal resting value.

The voltage-sensitive potassium channels respond to the depolarizing phase of the action potential by opening. But because of the delayed response of the n gates, the potassium channels begin to open at about the time sodium permeability returns to its normal low value (that is, when h gates close). Therefore, the repolarizing phase of the action potential is produced by a simultaneous decline of p_{Na} to its resting level and increase of p_{K} to a higher-than-normal level. During this time, $p_{\mathrm{Na}}/p_{\mathrm{K}}$ is actually *smaller* than its usual resting value. This reduction explains the undershoot of membrane potential below its resting value at the end of an action potential: E_{m} approaches nearer to E_{K} because p_{K} is still higher than usual but p_{Na} has returned to its resting state. Membrane potential returns to rest as the slow n gates finally respond to the repolarization by closing and returning p_{K} to its normal value.

The sequence of changes during an action potential is illustrated in Figure 5.10, and characteristics of the various gates are summarized in Table 5.1. An action potential is generated in the sensory neuron of the patellar reflex in the following way. Stretch of the muscle induces depolarization of the specialized sensory endings of the sensory neuron (probably by increasing the relative sodium permeability). This depolarization causes the m gates of voltage-sensitive sodium channels in the neuron membrane to open, initiating a regenerative increase in p_{Na}, which drives E_{m} up near E_{Na}. After a short delay, h gates respond to the depolarization by closing and potassium-channel n gates open. The combination of these delayed gating events drives E_{m} down near E_{K} and actually below the usual resting E_{m}. After another delay, the repolarization causes the h gates to open and the n gates to close, and the membrane returns to its resting state, ready to respond to a new depolarizing stimulus.

The scheme for the ionic changes underlying the nerve action potential was worked out in a series of elegant electrical experiments by A. L. Hodgkin and A. F. Huxley of Cambridge University. Chapter 6 describes those experiments in detail and presents a quantitative version of the scheme shown in Figure 5.10.

The refractory period

The existence of a refractory period would be expected from the gating scheme shown in Figure 5.10. When the h gates of the voltage-sensitive sodium channels are closed (states C and D in Figure 5.10), the channels cannot conduct Na^+, no matter what the state of the m gate. Under this condition, no amount of depolarization can cause the cell to fire an action potential. The h gates simply remain closed, preventing the Na^+ influx necessary to trigger the regenerative explosion. Only when enough time has passed for a significant number of h gates to reopen will the neuron be able to produce another action potential.

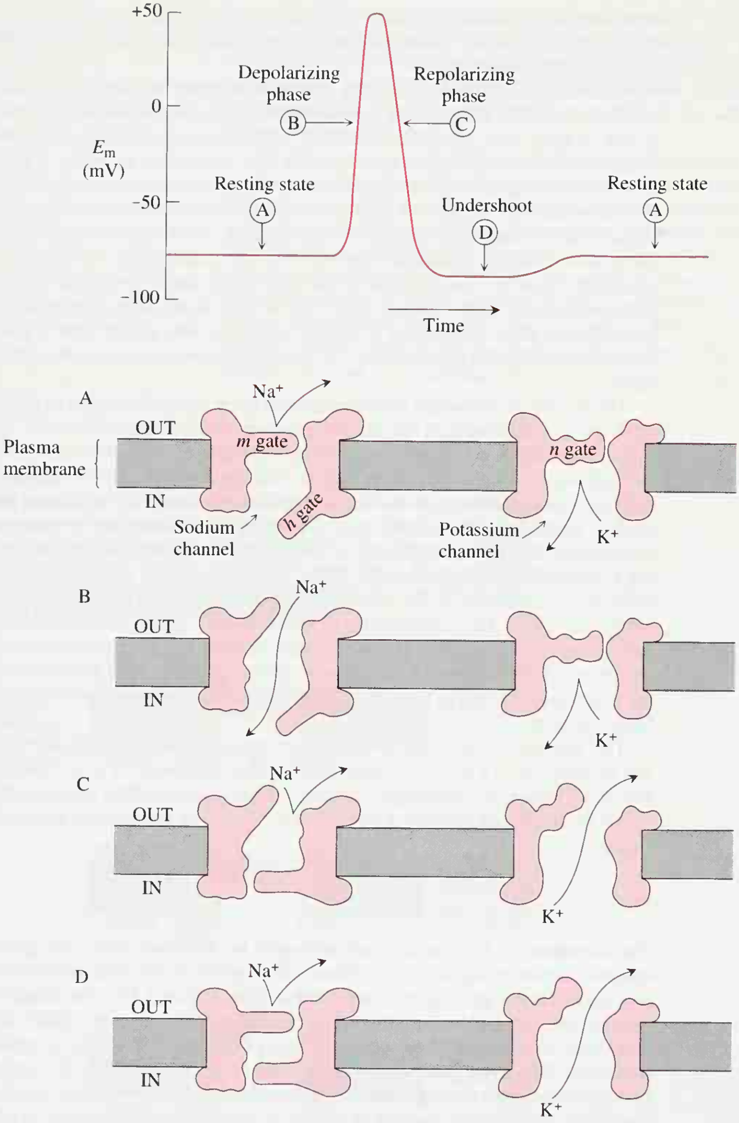

+50
0
-50
-100
E_m (mV)
Depolarizing phase
B
Repolarizing phase
C
Resting state
A
Undershoot
D
Resting state
A
Time
A
OUT
Plasma membrane
IN
Na+
m gate
h gate
Sodium channel
n gate
Potassium channel
K+
B
OUT
IN
Na+
K+
C
OUT
IN
Na+
K+
D
OUT
IN
Na+
K+

Table 5.1 Summary of responses of voltage-sensitive sodium and potassium channels to depolarization.

Type of Channel	Gate	Response to Depolarization	Speed of Response
Sodium	m gate	Opens	Fast
Sodium	h gate	Closes	Slow
Potassium	n gate	Opens	Slow

PROPAGATION OF AN ACTION POTENTIAL ALONG A NERVE FIBER

We can now see how an action potential arises as a result of a depolarizing stimulus, such as the muscle stretch in the case of the sensory neuron (see Fig. 5.1). How does the action potential travel from the ending in the muscle along the long, thin sensory fiber to the spinal cord? The answer to this question is inherent in the scheme for generation of the action potential just presented. As we saw, depolarization of greater than 10 to 20 mV from the normal resting level of membrane potential provides the stimulus for an action potential. The action potential itself represents a depolarization greatly in excess of this threshold level. Thus, once an action potential occurs at one end of a neuron, the strong depolarization will boost the neighboring region of the cell above the threshold, setting up a regenerative depolarization in that region. This action will, in turn, bring the next region above threshold, and so on.

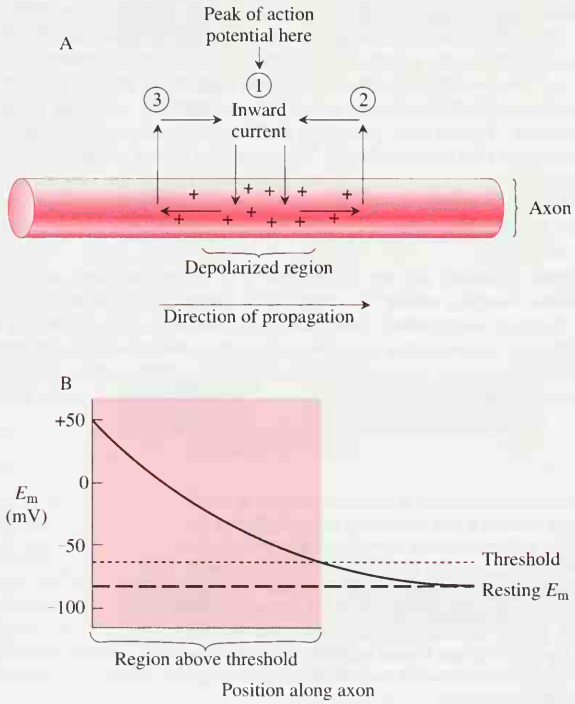
The action potential can be envisioned as a self-propagating wave of depolarization sweeping along the nerve fiber. When the sequence of permeability changes summarized in Figure 5.10 occurs in one region of a nerve membrane, it guarantees that the same gating events will be repeated in neighboring segments of membrane. In this manner, the cyclical changes in membrane permeability, and the resulting action potential, chew their

Figure 5.10
The states of voltage-sensitive sodium and potassium channels at various times during an action potential in a neuron. (A) At rest, neither channel is in a conducting state. (B) During the depolarizing phase of the action potential, the sodium channels open, but the potassium channels have not yet responded to the depolarization. (C) During the repolarizing phase, sodium permeability begins to return to its resting level as h gates have had sufficient time to respond to the depolarizing phase. At the same time, the potassium channels respond to the depolarization by opening. (D) During the undershoot, sodium permeability returns to its usual low level; potassium permeability, however, remains elevated because n gates respond slowly to the repolarization of the membrane. The resting state of the membrane is restored after h gates and n gates have sufficient time to respond to the repolarization.

way along the nerve fiber from one end to the other, as each subsequent segment of axon membrane responds to the depolarization of the preceding segment. This behavior is analogous to that of a lighted fuse, in which the heat generated in one segment of the fuse ignites its neighboring segment.

For a more formal description of propagation, consider the electrical currents that flow along a nerve fiber during an action potential. Imagine that we freeze an action potential in time while it is traveling down an axon, as shown in Figure 5.11A. At the peak of the action potential, an inward flow of current, carried by sodium ions, is generated. This flow is shown by the inward arrows at point 1 in Figure 5.11A. The region of axon occupied by the action potential

Figure 5.11
The decay of depolarization with distance from the peak of the action potential at a particular instant during the propagation of the action potential from left to right along the axon.



will be depolarized with respect to more distant parts of the axon, such as points 2 and 3. This difference in electrical potential means that a flow of depolarizing current will leave the depolarized region and flow along the inside of the nerve fiber.

In the discussion of the response to injected current in an axon (see Figs. 5.4 and 5.5), we saw that a voltage change produced by injected current decayed with distance from the point of injection. Similarly, the depolarization produced by the influx of sodium ions during an action potential becomes smaller with increasing distance from the region of membrane undergoing the action potential. This decay of depolarization with distance reflects the progressive leakage of the depolarizing current across the membrane, which is a leaky insulator. Figure 5.11B illustrates the profile of membrane potential that might be observed along the length of the axon at the instant that the action potential at point 1 reaches its peak. Note the region of axon over which the depolarization remains above the threshold for generating an action potential in that part of the membrane. If we "unfreeze" time and allow events to move forward, the region that is above threshold will generate its own action potential. This process will continue as the action potential sweeps along the axon, eventually bringing each successive segment of axon above threshold.

The flow of depolarizing current from the region undergoing an action potential is symmetrical in both directions along the axon (see Fig. 5.11A). Thus, current flows from point 1 to both points 2 and 3 in the figure. Nevertheless, the action potential in an axon typically moves in only one direction. This constraint occurs because the region just traversed by the action potential (for example, point 3) is experiencing the refractory period phase of the action potential cycle and cannot respond to the depolarization originating from the action potential at point 1. Of course, if a neurophysiologist creates an artificial situation (such as that shown in Figure 5.4) and stimulates an action potential in the middle of a nerve fiber, it will propagate in both directions along the fiber. The normal direction of propagation in an axon—the direction taken by normal action potentials—is called the **orthodromic** direction; an abnormal action potential propagating in the opposite direction is called an **antidromic** action potential.

FACTORS AFFECTING THE SPEED OF ACTION POTENTIAL PROPAGATION

The speed with which an action potential moves down an axon varies considerably from one axon to another, but generally falls in the range of 0.1 m/s to 100 m/s. What characteristics of an axon are important in determining the action potential propagation velocity? Consider Figure 5.11B again. Clearly, if the decay of depolarization with distance is relatively low, the region of axon brought above the threshold by an action potential at point 1 will expand. If the region above the threshold is larger, then an action potential at a particular location will create a new action potential at a greater distance down the axon and the rate at which the action potential moves down the fiber will increase.

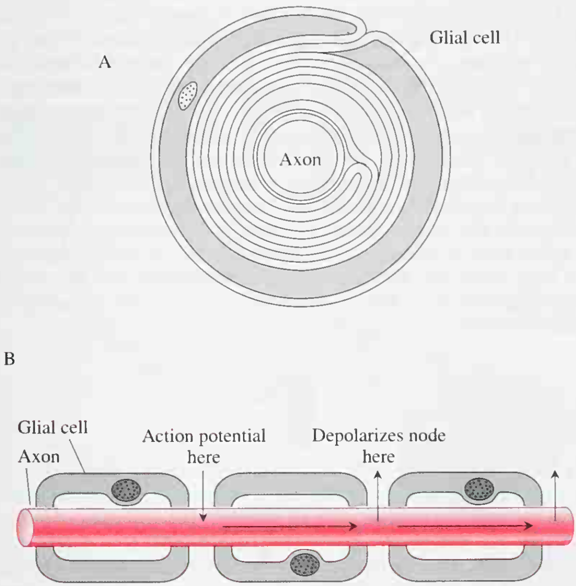
The rate of falloff of depolarization with distance will, in turn, depend on the relative resistance to current flow of the plasma membrane and the intracellular path down the axon. Recall from the discussion of an axon's response to an injection of current (see Fig. 5.5) that current flowing down the inside of axon at a particular point can take either of two paths: it can continue down the interior of the fiber or it can cross the membrane at that point. The portion of the current taking each path depends on the relative resistances of the two paths. If the resistance of the membrane could be increased or if the resistance of the path down the inside of the axon could be reduced, the path down the axon would be favored and a larger portion of the current would continue along the fiber's interior. In this situation, the depolarization resulting from an action potential would decay less rapidly along the axon, and the rate of propagation would increase.

Thus, two strategies can be employed to increase the speed of action potential propagation: (1) increase the electrical resistance of the plasma membrane to current flow, or (2) decrease the resistance of the longitudinal path down the inside of the fiber. Both strategies have been adopted in nature. Among invertebrate animals, the longitudinal resistance of the axon interior has been decreased by increasing the diameter of the axon. A fatter fiber offers a larger cross-sectional area to the internal flow of current; the effective resistance of this larger area is lower because the current can choose many parallel paths to continue down the axon's interior. For the same reason, electric power companies use large-diameter copper wire for the cables leaving a power-generating station; these cables must carry massive currents and thus must have low resistance to current flow to avoid burning up. Some invertebrate axons represent the neuronal equivalent of these power cables: axons up to 1 mm in diameter are found in some invertebrates. As might be expected, these giant axons are the fastest-conducting nerve fibers of the invertebrate world.

Vertebrate animals also demonstrate a wide variation in the size of axons, whose diameters range from less than 1 μm diameter to as large as 30 to 50 μm. Clearly, even the largest axons in a human nerve do not begin to rival the size of the giant axons of invertebrates. Nevertheless, the fastest-conducting vertebrate axons are actually faster than the giant invertebrate axons. Vertebrate animals have adopted the strategy of increasing the membrane resistance to current as well as increasing internal diameter. Their axons are wrapped with extra layers of insulating cell membrane, as shown in Figure 5.12A. To reach the exterior, electrical current must flow not only through the resistance of the axon membrane, but also through the cascaded resistance of the tightly wrapped layers of extra membrane. The cell that provides the spiral of insulating membrane surrounding the axon is a type of **glial cell**, a non-neuronal supporting cell of the nervous system that provides a sustaining mesh in which the neurons are embedded.

The insulating sheath around the axon is called **myelin**. By increasing the resistance of the path across the membrane, the myelin sheath forces a larger

Figure 5.12
The propagation of an action potential along a myelinated nerve fiber. (A) A cross section of a myelinated axon, showing the spiral wrapping of the glial cell membrane around the axon. (B) The depolarization from an action potential at one node spreads along the interior of the fiber because the insulating myelin prevents the leakage of current across the plasma membrane.



portion of the current generated by a voltage change to move down the interior of the fiber. This process increases the spatial spread of a depolarization along the axon and increases the propagation rate of the action potential. To set up a new action potential at a distant point along the axon, however, the influx of sodium ions carrying the depolarizing current during the initiation of the action potential must have access to the axon membrane. To provide that access, periodic breaks appear in the myelin sheath, called **nodes of Ranvier**, at regular intervals along the length of the axon (Fig. 5.12B). Thus, the depolarization resulting from an action potential at one node of Ranvier spreads along the interior of the fiber to the next node, where it initiates a new action potential. The action potential leaps along the axon, jumping from one node to the next. This form of action potential conduction is called **saltatory conduction**, and it produces a dramatic improvement in the speed with which a thin axon can conduct an action potential along its length.

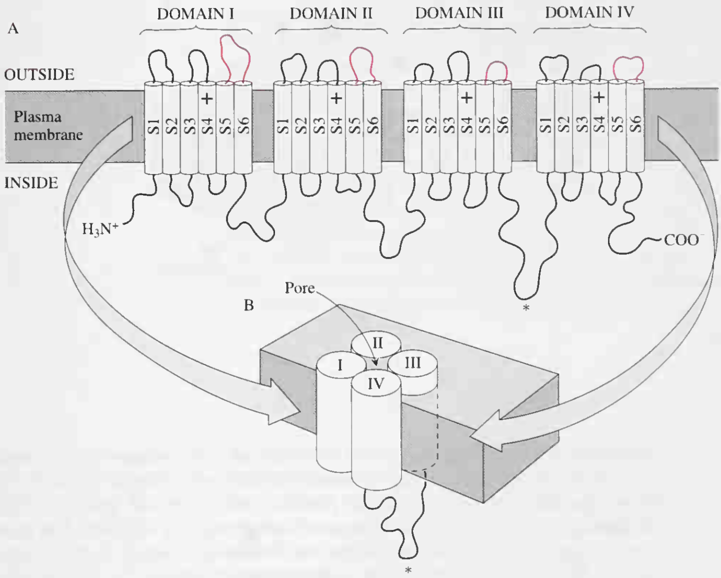
The myelin sheath also influences the axon's behavior as an electrical capacitor. Recall from chapter 3 that the cell membrane can be viewed as an insulating barrier that separates two conducting compartments (the ICF and ECF). Thus, it forms a capacitor. The capacitance, or charge-storing ability, of a capacitor is inversely related to the distance between the conducting plates: the smaller the distance, the greater the number of charges that can be stored on the capacitor in the presence of a particular voltage gradient. When the myelin sheath wrapped around an axon increases the distance between the conducting ECF and ICF, the effective capacitance of the membrane decreases. As a result, a smaller number of charges must be added to the inside of the membrane to reach a particular level of depolarization. (If you are uncertain why this statement is true, review the calculation of the number of charges on a membrane at a particular voltage found in chapter 3.) An electrical current is defined as the rate of charge movement—that is, the number of charges per second. In the presence of a particular depolarizing current, a given level of voltage will be reached faster on a small capacitor than on a large capacitor. Because the myelin decreases the membrane capacitance, a depolarization will spread more rapidly, as well as farther, in the presence of myelin.

MOLECULAR PROPERTIES OF THE VOLTAGE-SENSITIVE SODIUM CHANNEL

Ion channels are proteins and, as with all proteins, the sequence of amino acids making up the protein of a particular ion channel is encoded by a particular gene. Thus, we can study the properties of ion channels by applying techniques of molecular biology to isolate and analyze the corresponding genes. This strategy has been applied to a variety of ion channels, including the voltage-sensitive sodium channel that underlies the action potential.

The sodium channel is a large protein, containing some 2000 individual amino acids. A model of how it folds up into a three-dimensional structure has been developed (Fig. 5.13). According to the model, the sodium-channel protein consists of four distinct regions, called domains. Each domain includes six separate segments, labeled S1 through S6, that extend completely across the plasma membrane (transmembrane segments). In this way, the protein threads its way through the membrane six times within each domain (see Fig. 5.13). The amino-acid sequences of the six transmembrane segments within a particular domain are similar to the corresponding segments in the other domains. As a result, the overall structure of the channel can be regarded as a series of six transmembrane segments, repeated four times.

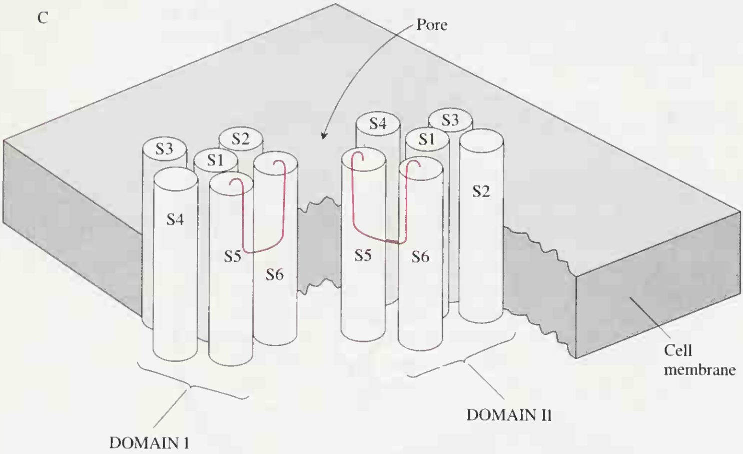
Figure 5.13
The molecular structure of a voltage-sensitive sodium channel. (A) The molecule consists of four domains of similar make-up, labeled with Roman numerals; each domain has six transmembrane segments (S1–S6). The highly positively charged segment S4 is indicated in each domain by +. The linkage between domains III and IV, indicated by *, is involved in inactivation gating. In A, the domains are shown in a linear arrangement, for clarity. In reality, the domains likely form a circular arrangement with the pore at the center (B).



The four domains are thought to aggregate in a circular pattern (see Fig. 5.13B) to form the pore of the channel. The lining of the pore determines the permeation properties of the channel and dictates the channel's selectivity for sodium ions. Interestingly, the lining appears to be made up of the external loop connecting segments S5 and S6 within each of the four domains (shown in color in Figure 5.13A). To form the transmembrane pore through which sodium ions cross the membrane, this external loop must fold down into the pore in the manner shown in Figure 5.13C.

What part of the protein detects changes in the membrane potential and thus imparts voltage-sensitivity to the channel? Attention has focused on the fourth transmembrane segment of each domain, segment S4

Figure 5.13 (continued)
The extracellular loop shown in red in C may fold in as indicated to line the entry to the pore and thus control the ionic selectivity of the channel.



(marked with a "+" in Figure 5.13A). Segment S4 includes an unusual accumulation of positive charge (because of positively charged arginine and lysine residues in that part of the protein), which should give it a high sensitivity to the electric field across the membrane. In addition, the positive charges in S4 are located within the membrane, which is the correct position to be acted upon by the transmembrane voltage. To test the idea that the charges in S4 act as the voltage sensors, W. Stühmer and co-workers constructed artificial sodium channels by altering the DNA so that one or more of the arginines or lysines in S4 were replaced with neutral or negatively charged amino acids. These artificial channels were less voltage-dependent than the normal channels, suggesting that the S4 charges are the voltage sensors that detect depolarization of the membrane and activate the opening of the m gate.

Another important issue is to establish the identity of the sodium inactivation gate, the h gate. In this case, Stühmer and co-workers found that the part of the protein connecting domains III and IV (marked with a "*" in Figure 5.13) is important. If that region was deleted or altered, the inactivation process was greatly impaired, although activation seemed normal. This part of the protein lies on the intracellular side of the membrane, where the h gate in our earlier diagrams of sodium channels was positioned.

MOLECULAR PROPERTIES OF VOLTAGE-DEPENDENT POTASSIUM CHANNELS

The DNA coding for various other voltage-activated channels, including voltage-activated potassium channels, has also been analyzed to reveal the sequence of amino acids making up those proteins. Interestingly, these voltage-activated channels all have similar (though, of course, not identical) amino-acid sequences, especially in segment S4, which seems to impart the voltage sensitivity. In this way, voltage-activated channels represent a family of proteins coded by related genes that probably arose during the course of evolution from a single ancestral ion-channel gene that existed eons ago.

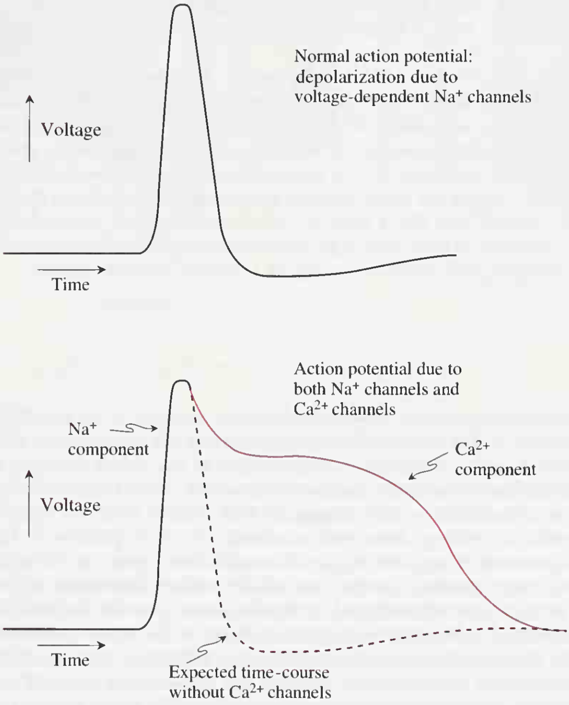
Potassium channel genes, however, encode proteins that are much smaller than sodium channels. In fact, the protein encoded by these genes seems to correspond to a single member of the four domains present in the voltage-activated sodium channel (see Fig. 5.13). Functional potassium channels are thought to be formed by the aggregation of four of these individual protein subunits, giving the entire channel an arrangement similar to that of the sodium channel (see Fig. 5.13B). In the sodium channel, the four domains are combined to form one large, continuous protein molecule; in the potassium channel, each domain consists of a separate protein subunit.

CALCIUM-DEPENDENT ACTION POTENTIALS

In our discussion of nervous system evolution in chapter 2, we described action potentials in the single-celled *Paramecium* and the multicellular *Obelia*. In these organisms, the depolarizing upstroke of the action potential is caused by an influx of positively charged calcium ions, rather than the influx of sodium ions described in this chapter. As with sodium ions, the equilibrium potential for calcium ions (with a valence of +2) is positive. If the membrane potential is negative and a calcium channel opens, an influx of calcium will enter the cell. In the case of the sodium-dependent action potential, sodium channels activated by depolarization provide the basis for the regenerative all-or-nothing depolarizing phase of the action potential. Similarly, in the case of calcium-dependent action potentials, calcium channels that open upon depolarization underlie the depolarizing phase of the action potential. Depolarization opens calcium channels, which permit the influx of positively charged calcium ions, which in turn produces greater depolarization and opens additional calcium channels (see Figure 5.7 for the analogous situation with depolarization-activated sodium channels).

Voltage-dependent calcium channels are found in most neurons. In some neurons, they contribute significantly to the action potential. Figure 5.14 compares the waveform of the sodium-dependent action potential and the waveform of an action potential with a component caused by calcium influx. Often, the depolarization produced by calcium influx is slower and more

Figure 5.14
A comparison between the action potentials in neurons without a contribution from voltage-dependent calcium channels (top) and in neurons with a calcium component (bottom). The rising phase of the action potential on the bottom (black portion) derives from depolarization-activated sodium channels, and the dashed black line shows the expected time-course of the action potential in the absence of calcium channels. The red line shows the plateau depolarization caused by the opening of voltage-sensitive calcium channels.



sustained than the “spike-like” action potential generated by sodium and potassium channels alone. Because the voltage-activated calcium channels usually inactivate more slowly than voltage-activated sodium channels, they produce a more sustained influx of positive charge, and thus a more prolonged depolarization. In neurons with a calcium-dependent component, the action potential shows a rapid upstroke caused by the opening of sodium channels, followed by a longer-duration plateau phase produced by the voltage-dependent calcium channels.

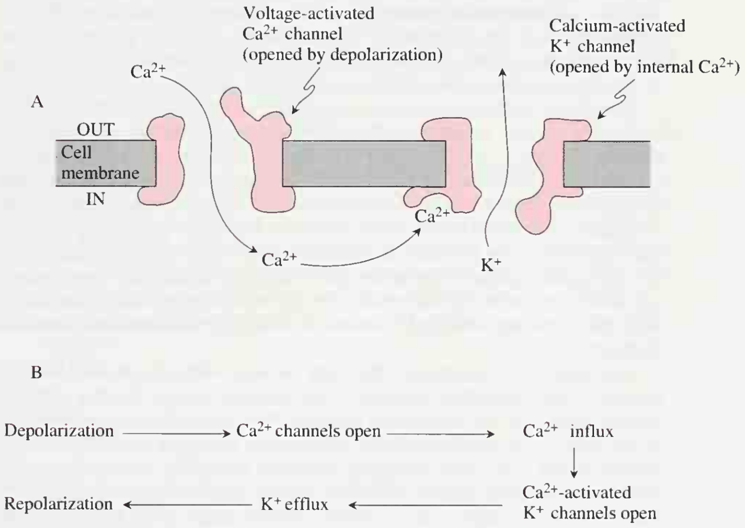
The influx of calcium ions through voltage-dependent calcium channels has functional consequences beyond its contribution to the action potential. The increase in the intracellular concentration of calcium that results from the influx represents an important cellular signal that allows depolarization of a cell to be coupled to the triggering of internal cellular events. For example, an increase in intracellular calcium triggers the release of neurotransmitter from the presynaptic terminal when an action potential arrives at the synaptic junction between two neurons (described in detail in chapter 7). Internal calcium accumulation also activates other kinds of ion channels.

In addition to the potassium channels opened by depolarization, neurons frequently possess potassium channels that are opened by an increase in internal calcium. The activation scheme for calcium-activated potassium channels is summarized in Figure 5.15. Calcium-activated potassium channels can contribute to action potential repolarization in neurons that include a calcium component in the action potential (see, for example, Fig. 5.14). As discussed earlier, an increase in potassium permeability partly accounts for the repolarizing phase of the action potential and produces the hyperpolarizing undershoot after repolarization. The increase in p_K can be accomplished with either voltage-activated channels or with calcium-activated potassium channels.

One important functional difference between voltage-activated and calcium-activated potassium channels is the amount of time that the channels remain open after the membrane potential has returned to its negative level at the end of the action potential. The action potential undershoot corresponds to the time after an action potential when the voltage-dependent potassium channels remain open but sodium permeability has returned to rest. Because the ratio p_{Na}/p_K is *smaller* than its usual value, the membrane potential is driven even nearer to the potassium equilibrium potential. The period of hyperpolarization during the undershoot ends when the voltage-dependent potassium channels close in response to repolarization, which takes a few milliseconds or less. In contrast, calcium-activated potassium channels remain open for as long as the intracellular calcium level remains elevated after the action potential. This period can be hundreds of times longer than the undershoot produced by the voltage-dependent potassium channels (Fig. 5.16). This longer-lasting hyperpolarization is called the **after hyperpolarization** to distinguish it from the undershoot.

The presence of an after hyperpolarization requires both a significant calcium influx during the action potential (to increase the internal calcium concentration) and significant numbers of calcium-activated potassium channels (to increase potassium permeability in response to the increase in internal calcium level). Not all neurons possess these requirements and thus do not show prolonged after hyperpolarizations. In neurons that experience only a small component of calcium influx during a single action potential, after hyperpolarizations may occur if the cell fires a rapid burst of action potentials. In such a case, the internal calcium contributed by each action potential may accumulate to reach the level necessary to open

Figure 5.15
Activation of potassium channels by internal calcium ions. (A) Upon depolarization, voltage-dependent calcium channels open and calcium ions enter the cell from the ECF. The calcium ions then bind to and open calcium-activated potassium channels, which enable potassium ions to exit from the cell. (B) A summary of the sequence of events leading to activation of calcium-activated potassium channels.



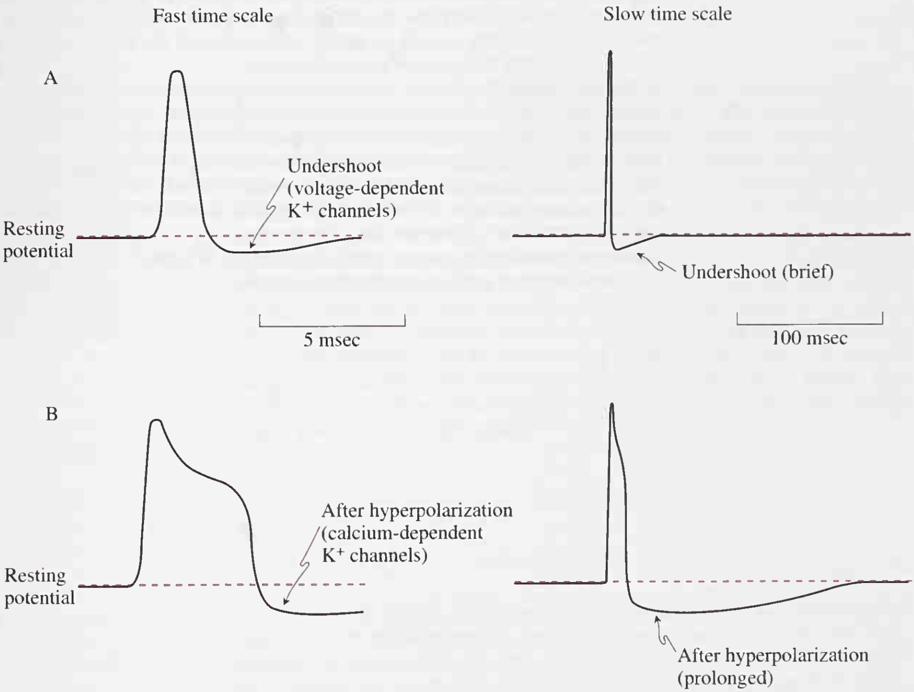
calcium-activated potassium channels. The after hyperpolarization helps to determine the temporal patterning of action potentials, because the long period of increased potassium permeability makes it more difficult for the neuron to fire action potentials in a rapid series. In neurons that require a burst of several action potentials to initiate the after hyperpolarization, the calcium-activated potassium channels can aid in terminating the burst. We will encounter such a mechanism for regulating burst duration, for example, when we discuss neuronal circuits controlling locomotion in chapter 10.

SUMMARY

The basic long-distance signal of the nervous system is a self-propagating depolarization called the action potential. It arises through a sequence of voltage-dependent changes in the ionic permeability of the neuron membrane. This

Figure 5.16

The time-course of undershoot compared with the time-course of after hyperpolarization due to calcium-activated potassium channels. (A) The action potential of a neuron with only voltage-dependent sodium and potassium channels. (B) The action potential of a neuron with voltage-dependent calcium channels and calcium-activated potassium channels in addition to the usual voltage-dependent sodium and potassium channels. The left-hand traces in both A and B show the action potential on a fast time scale (milliseconds), while the right-hand traces show the same action potentials on a slower time scale (hundreds of milliseconds).



voltage-dependent behavior of the membrane is related to the presence of gated sodium and potassium channels. The conducting state of the sodium channels is controlled by m gates, which are closed at the usual resting E_m and open rapidly upon depolarization, and by h gates, which remain open at the usual resting E_m and close slowly upon depolarization. The voltage-sensitive potassium channels are controlled by a single gate, the n gate, which remains closed at the resting E_m and opens slowly upon depolarization. In response to depolarization, p_{Na} increases dramatically as m gates open, and E_m rises to near

E_{Na}. After a delay, h gates close, restoring p_{Na} to a low level, and n gates open, increasing p_{K}. As a result, $p_{\mathrm{Na}}/p_{\mathrm{K}}$ falls below its normal resting value, and E_{m} declines to near E_{K}. The resulting repolarization restores the membrane to its resting state.

The behavior of the voltage-dependent sodium and potassium channels can explain several facets of the action potential: (1) why depolarization stimulates the generation of an action potential; (2) why action potentials are all-or-nothing events; (3) how action potentials propagate along nerve fibers; (4) why the membrane potential becomes positive at the peak of the action potential; (5) why the membrane potential is transiently more negative than usual at the end of an action potential; and (6) why a refractory period follows the firing of an action potential.

Action potentials of some neurons include components contributed by voltage-dependent calcium channels, which open upon depolarization like voltage-dependent sodium channels but permit influx of calcium ions. This influx can, in turn, increase the intracellular concentration of calcium. Calcium-activated potassium channels open when internal calcium levels are elevated, contributing to the repolarization of the action potential. Calcium-activated potassium channels can also produce a prolonged elevation of potassium permeability during which the membrane potential is more negative than the usual resting membrane potential.

6

The Action Potential: Voltage-Clamp Experiments

In chapter 5, we discussed the basic membrane mechanisms underlying the generation of the action potential in a neuron. All properties of the action potential could be explained by the actions of voltage-sensitive sodium and potassium channels in the plasma membrane, both of which behave as though voltage-activated gates control permeation of ions through the channel. In this chapter, we will discuss the experimental evidence that gave rise to this scheme for explaining the action potential. The fundamental experiments were performed by Alan L. Hodgkin and Andrew F. Huxley during the period 1949–1952, with Bernard Katz participating in some of the early work. The Hodgkin–Huxley model of the nerve action potential is based on electrical measurements of the flow of ions across the membrane of an axon, using a technique known as voltage clamp. We will begin by describing how the voltage clamp works, and then discuss the observations Hodgkin and Huxley made and their arrival at the gated ion channel model.

THE VOLTAGE CLAMP

As we saw in chapter 5, the permeability of an excitable cell membrane to sodium and potassium depends on the voltage across the membrane. Voltage-induced permeability changes occur at different speeds for the different ionic "gates" on the voltage-sensitive channels, which means that membrane permeability to sodium, for example, is a function of two variables: voltage and time. To study this permeability quantitatively, we must gain experimental control of one of these two variables. We can then hold it constant and see how permeability varies as a function of the other variable. The voltage clamp is a recording technique that holds membrane voltage at a constant value; that is, the membrane potential is "clamped" at a particular level. We can then measure the membrane current flowing at that constant membrane voltage and use the time-course of changes in membrane current as an index of the time-course of the underlying changes in membrane ionic conductance.

Figure 6.1

A schematic diagram of a voltage-clamp apparatus.

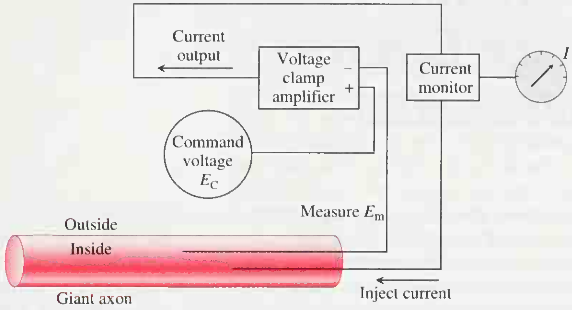


Figure 6.1 diagrams the apparatus used to voltage-clamp an axon. Two long, thin wires are threaded longitudinally down the interior of an isolated segment of axon. One wire measures the membrane potential, as was done in a number of previous examples in earlier chapters using intracellular microelectrodes; this wire is connected to one of the inputs of the voltage-clamp amplifier. The other wire passes current into the axon and is connected to the output of the voltage-clamp amplifier. The other input of the amplifier is connected to an external voltage source—the command voltage—that the experimenter controls. The command voltage is so named because its value determines the value of resting membrane potential that will be maintained by the voltage-clamp amplifier.

The amplifier in the voltage-clamp circuit is wired to feed a current into the axon that is proportional to the difference between the command voltage and the measured membrane potential, $E_C - E_m$. If that difference is zero (that is, if $E_m = E_C$), the amplifier generates no current, and E_m remains stable. If E_m does not equal E_C, the amplifier passes a current into the axon to make the membrane potential move toward the command voltage. For example, if E_m is -70 mV and E_C is -60 mV, then $E_C - E_m$ is a positive number. Because the amplifier passes a current that is proportional to that difference, the current will also be positive. In this case, the injected current will move positive charges into the axon and depolarize the membrane toward E_C. This process would continue until the membrane potential equals the command potential of -60 mV. On the other hand, if E_C were more negative than E_m, $E_C - E_m$ would be a negative number, and the injected current would be negative. In this case, the current would hyperpolarize the axon until the membrane potential equals the command voltage.

MEASURING CHANGES IN MEMBRANE IONIC CONDUCTANCE USING THE VOLTAGE CLAMP

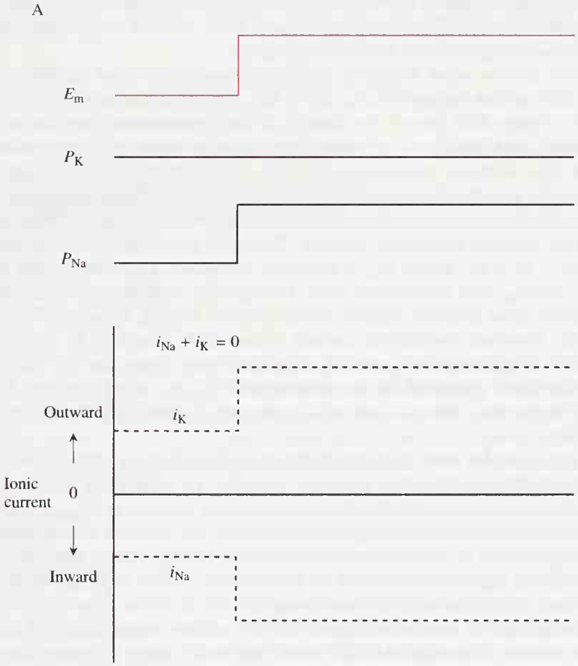
Insertion of a current monitor into the output line of the amplifier allows us to measure the amount of current passed by the amplifier to keep the membrane voltage equal to the command voltage. How does this measured current provide information about changes in ionic current and, therefore, changes in ionic conductance of the membrane?

First, let's review what happens to membrane current and membrane potential without the voltage clamp, using the principles discussed in chapters 4 and 5. Figure 6.2A shows the changes in transmembrane ionic current (dashed traces) and membrane potential (red trace) in response to a stepwise increase in p_{Na}, with p_K remaining constant (black traces). Under resting conditions, the steady-state membrane potential will fall between E_{Na} and E_K, at the membrane voltage at which the inward sodium current exactly balances the outward potassium current. The total membrane current will be zero ($i_{Na} + i_K = 0$). When p_{Na} is suddenly increased, the steady state is perturbed, and i_{Na} will increase as well. This greater sodium influx causes E_m to become more positive relative to its original resting value. With depolarization, however, potassium current increases in response to the increasing difference between E_m and E_K. The membrane potential will reach a new steady state, governed by the new ratio of p_{Na}/p_K, at which both i_{Na} and i_K are larger than their initial values, but once again exactly balance one another.

Next, let's consider what happens if the same change in p_{Na} occurs under voltage clamp (Fig. 6.2B). Now we must consider an additional source of current: the current provided by the voltage-clamp apparatus (i_{clamp}). Suppose we set the command voltage, E_C, equal to the normal steady-state membrane potential of the cell and turn on the voltage-clamp apparatus. In this situation, E_m is already equal to E_C and the current injected by the voltage-clamp apparatus will be zero. Suppose that at some time after we turn on the apparatus, a sudden increase in the sodium permeability of the membrane occurs. This sodium influx would normally cause the membrane potential to take up a new steady-state value closer to the sodium equilibrium potential; that is, the cell would depolarize because of the greater inward sodium current flowing across the membrane. The voltage-clamp circuit will detect the depolarization as soon as it begins, however, and its amplifier will inject negative current into the axon to counter the increased sodium current (see the dashed trace labeled i_{clamp} in Figure 6.2B). The voltage clamp continues to inject this holding current to maintain E_m at its usual resting value as long as the increased sodium permeability persists, so that E_m remains equal to E_C (red trace). Thus, the injected current will be equal in magnitude to the increase in sodium current resulting from the increase in sodium permeability. Notice the lack of change in i_K, because no change occurs in E_m (or in p_K).

If the potassium permeability—rather than the sodium permeability—were to undergo a stepwise increase from its normal resting value, then the

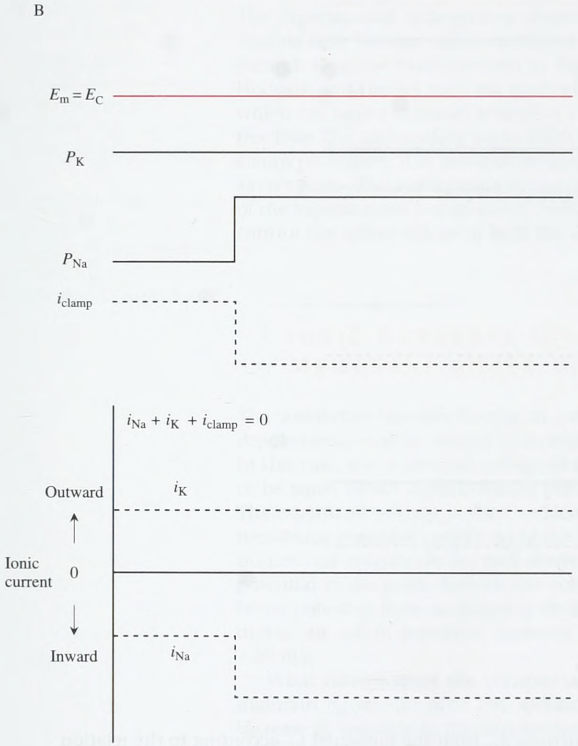
Figure 6.2
Ionic currents flowing in response to a stepwise change in p_{Na}, with or without a voltage clamp. (A) Without the voltage clamp, both i_{Na} and i_K increase in response to the increase in p_{Na}, and a new steady-state membrane potential (red trace) is reached at a more depolarized level.



voltage-clamp apparatus will respond as shown in Figure 6.3. In this case, the increased potassium permeability would normally force E_m to become more *negative* (that is, toward E_K), and the cell would *hyperpolarize*. The voltage-clamp amplifier, however, injects a depolarizing current of the correct magnitude to counteract the hyperpolarizing potassium current leaving the cell. As a result, the current injected by the voltage clamp gives a direct measure of the change in ionic current resulting from a change in membrane permeability to an ion.

How do we relate the measured change in membrane current to the underlying change in membrane permeability? Recall from chapter 4 that

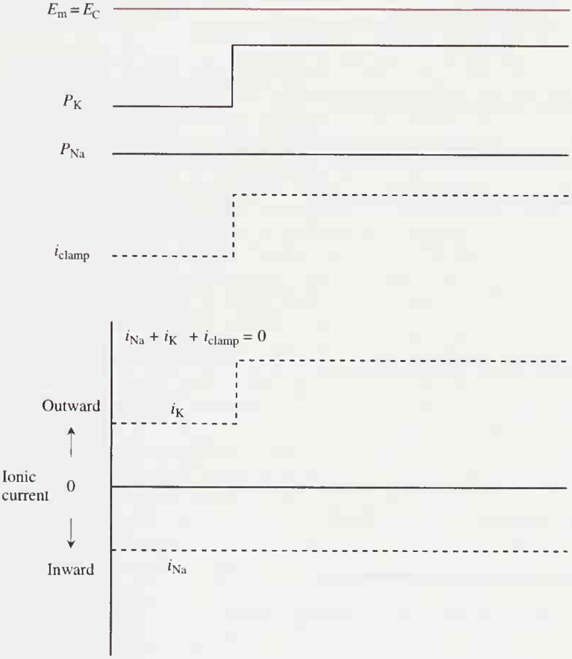
Figure 6.2 (continued)
(B) With the voltage clamp, the membrane potential remains constant because the voltage-clamp apparatus injects current (i_{clamp}) that compensates for the increased sodium current. The potassium current remains constant because neither p_K nor E_m changes.



the ionic current carried by a particular ion is given by the product of the membrane conductance to that ion and the voltage driving force for that ion; the latter value is the difference between the actual value of membrane potential and the equilibrium potential for the ion. For example, for sodium ions,

$$i_{Na} = g_{Na}(E_m - E_{Na}) \tag{6.1}$$

Figure 6.3
Changes in ionic current and injected current after a stepwise change in p_K under a voltage clamp. Potassium current increases in response to the increase in p_K, but the voltage-clamp amplifier injects compensating current to hold E_m constant.



We can calculate g_{Na} from the measured i_{Na} according to the relation

$$g_{Na} = i_{Na} / (E_m - E_{Na}) \tag{6.2}$$

In this calculation, E_m is set by the voltage clamp, and E_{Na} can be computed from the Nernst equation or measured experimentally by setting E_C to different values and determining when no change occurs in the ionic current after a change in g_{Na} (that is, when $E_m - E_{Na} = 0$). Equation (6.2) provides a straightforward way to obtain the time-course of a change in membrane ionic conductance from the time-course of the change in ionic current. As discussed in chapter 4, conductance is not the same as permeability.

For changes in permeability like those underlying the action potential, however, we can treat the two parameters as having the same time-course.

THE SQUID GIANT AXON

The experimental arrangement diagrammed in Figure 6.1 was technically feasible only because nature provided neurophysiology with an axon large enough to allow experimenters to thread a pair of wires down its inside. Hodgkin and Huxley used the giant axon from the nerve cord of the squid, which can have a diameter as large as 1 mm. It is large enough to be dissected free from the surrounding nerve fibers and then be subjected to the voltage-clamp procedure. It is possible to squeeze the normal ICF out of the giant axon's fiber—like toothpaste out of a tube—and replace it with artificial ICF of the experimenter's concoction. This technique allows the experimenter to control the compositions of both the ICF and ECF.

IONIC CURRENTS ACROSS AN AXON MEMBRANE UNDER VOLTAGE CLAMP

The membrane currents flowing in a squid giant axon during a maintained depolarization can be studied in an experiment like that shown in Figure 6.4. In this case, the command voltage to the voltage-clamp amplifier is first set to be equal to the normal resting potential of the axon (−60 to −70 mV). The command voltage is then suddenly increased to −20 mV, driving the membrane potential rapidly up to the same depolarized value. A depolarization of this magnitude lies well above the threshold for eliciting an action potential in the axon. Because the voltage-clamp circuit prevents the membrane potential from undergoing the usual sequence of changes that occur during an action potential, however, the membrane potential is held at −20 mV.

What current must the voltage-clamp amplifier inject into the axon to maintain E_m at −20 mV? The sodium permeability of the membrane will increase in response to the depolarization, and an increased sodium current will enter the axon through the increased membrane conductance to sodium. Without the voltage clamp, a regenerative depolarization would drive E_m up near E_{Na}, to approximately +50 mV. To counter this further depolarization, the voltage-clamp amplifier must inject a hyperpolarizing current during the strong depolarizing phase of the action potential. With time, however, the sodium permeability of the membrane declines, and the potassium permeability increases in response to membrane depolarization. Normally, this event would drive E_m down near E_K. To counter this tendency and maintain E_m at −20 mV, the voltage clamp must pass a depolarizing current that lasts as long as the elevated potassium permeability. Thus, in response to a depolarizing step above threshold, the membrane of an excitable cell would be expected to show a transient inward current followed by a longer-duration outward current. The voltage-clamp records of membrane current illustrating this sequence of changes are shown in Figure 6.4.

What is the evidence that the initial inward current is carried by sodium ions? This can be established by measuring the membrane current resulting from a series of voltage steps of different amplitudes. As we have seen previously, if the clamped value of membrane potential were equal to the sodium equilibrium potential, there would be no driving force for a net sodium current across the membrane. Therefore, if the initial current is carried by sodium ions, that component of the current should disappear when the command voltage equals E_{Na}. A sample of membrane current observed in response to a voltage step to E_{Na} is shown in Figure 6.5. The initial component of inward current disappears in this situation, leaving only the late outward current.

When Hodgkin and Huxley systematically varied E_{Na} by altering the external sodium concentration, they found that the membrane potential at which the early current component disappeared was always E_{Na}. This finding represents strong evidence that the inward component of current in response to a depolarization is carried by sodium ions. It also agrees with earlier

Figure 6.4
A diagram of the current injected by a voltage-clamp amplifier into an axon in response to a voltage step from −70 to −20 mV.

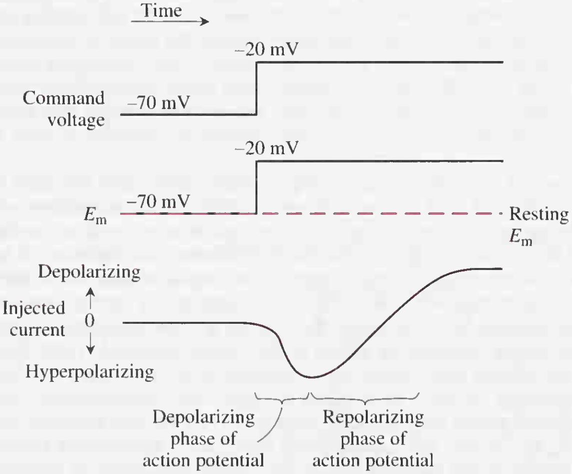
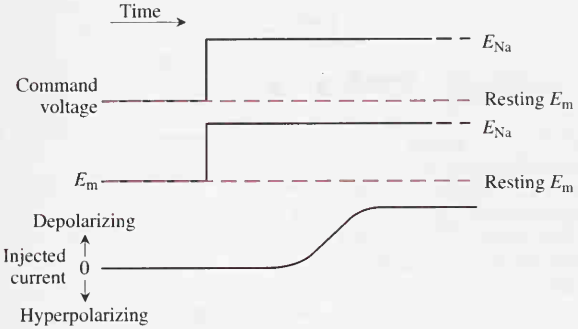


Figure 6.5
A diagram of the current injected by a voltage-clamp amplifier into an axon in response to a voltage step from the normal resting membrane potential to the sodium equilibrium potential. The initial sodium current is absent because no driving force exists for the sodium current when E_m equals E_{Na}.

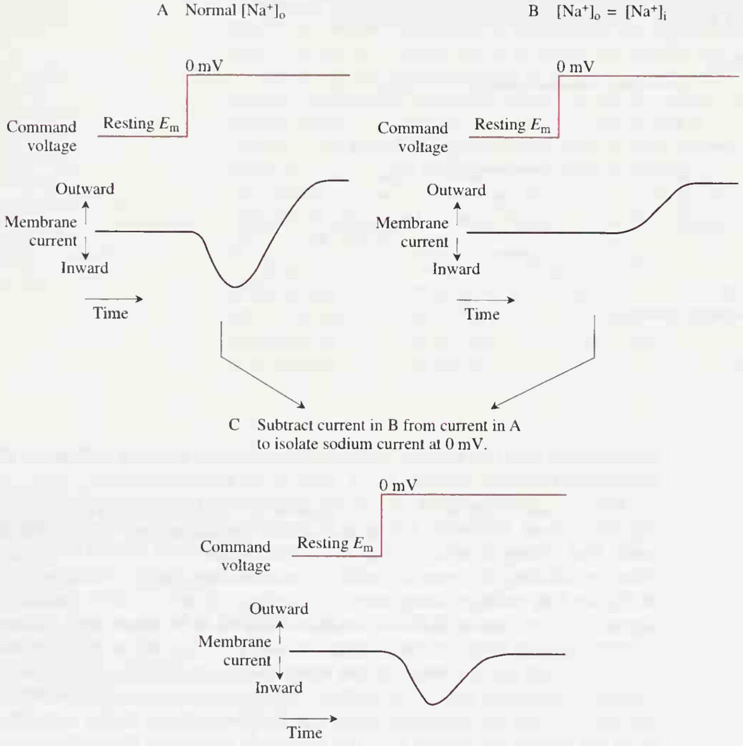


observations that the external sodium concentration strongly influences the membrane potential reached at the peak of the action potential.

The two components of membrane current can be separated by comparing the current following a step to a particular voltage in two situations: when that voltage is equal to E_{Na}, and when E_{Na} has been moved to another value by altering the external sodium concentration. In the example given in Figure 6.6, voltage-clamp steps are made to 0 mV in ECF containing normal sodium and in ECF with sodium reduced to be equal with internal sodium concentration. In the normal-sodium ECF, E_{Na} will be positive relative to the command voltage; in the reduced-sodium ECF, E_{Na} will equal the command potential and no net sodium current across the membrane will be observed. When the observed current in reduced-sodium ECF is subtracted from the current in normal ECF, the difference represents the sodium component of membrane current generated in response to the step depolarization to 0 mV (Fig. 6.6C). If the membrane currents in this situation are converted to membrane conductance according to Equation (6.2), the result gives the time-course of the membrane sodium and potassium conductances in response to a voltage-clamp step to 0 mV. This procedure can be repeated for a series of different values of the command potential and E_{Na}, generating a full characterization of the sodium and potassium conductance changes as a function of both time and membrane voltage.

The increase in sodium conductance in response to depolarization is transient, even if the depolarization endures. The increasing phase is called **sodium activation**, and the delayed decline is called **sodium inactivation**. We will discuss activation first and return later to the mechanism of inacti-

Figure 6.6
The procedure for isolating the sodium component of membrane current by varying external sodium concentration to alter the sodium equilibrium potential.



vation. The onset of the increase in potassium conductance occurs more slowly than sodium activation and does not inactivate upon maintained depolarization. Thus, at least on the brief time scale relevant to the action potential, potassium conductance remains high for the duration of the depolarizing voltage step.

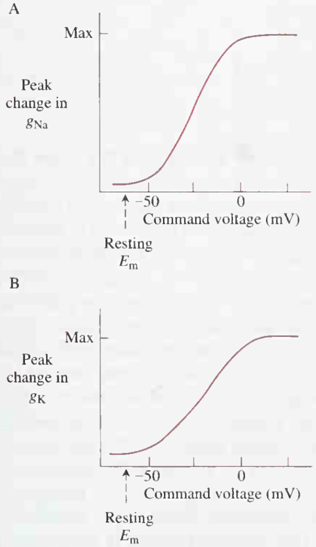
This rather involved procedure has been simplified considerably by the discovery of specific drugs that block the voltage-sensitive sodium channels and other drugs that block the voltage-sensitive potassium channels. The most commonly used sodium-channel blockers are the biological toxins tetrodotoxin and saxitoxin. Both interact with specific sites inside the aqueous pore of the channel and physically plug the channel to prevent sodium movement. Potassium-channel blockers include tetraethylammonium (TEA) and 4-aminopyridine (4-AP). The isolated behavior of the sodium current could be studied by treating an axon with TEA, for example, while the isolated potassium current could be studied in the presence of tetrodotoxin.

THE GATED ION CHANNEL MODEL

Membrane potential and peak ionic conductance

Hodgkin and Huxley discovered that the peak magnitude of the conductance change produced by a depolarizing voltage-clamp step depended on the size of the step. This finding established the voltage dependence of the sodium and potassium conductances of the axon membrane. Figure 6.7 shows the form of this dependence for sodium and potassium conductances. Note the steepness of the curves in both cases. For example, a voltage step to −50 mV barely increases g_{Na}, but a step to −30 mV produces a large rise in g_{Na}.

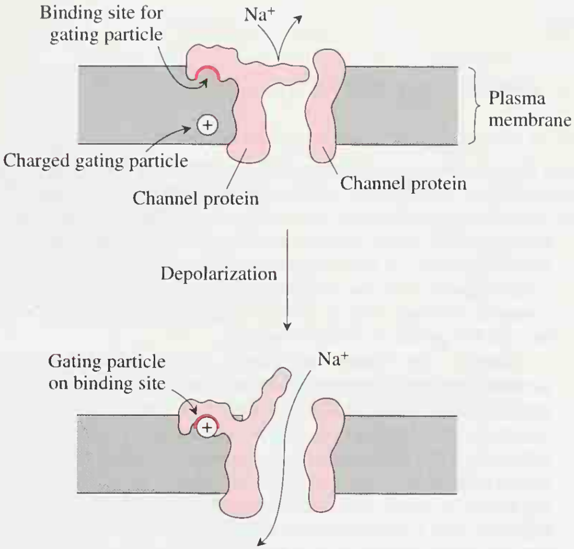
Figure 6.7
The voltage-dependence of peak sodium (A) and potassium (B) conductances as a function of the amplitude of a maintained voltage step.



Hodgkin and Huxley suggested a simple model that could account for the voltage sensitivity of both sodium and potassium conductances. Their model assumes that many individual ion channels, each having a small ionic conductance, determine the behavior of the entire membrane as measured with the voltage-clamp procedure. Each channel is assumed to have two conducting states: an open state in which ions are free to cross through the pore, and a closed state in which the pore is blocked. Thus, the channels behave as if a gate controls access to the pore. Under this scheme, changing the membrane potential alters the probability that a channel will enter the open, conducting state. Depolarization increases the probability that a channel is open, meaning that a larger fraction of the total population of channels is open and the total membrane conductance to that ion increases. The maximum conductance is reached when all channels are open, in which case further depolarization can have no greater effect.

If the conducting state of the channel is to depend on transmembrane voltage, some charged entity (either a part of the channel protein or a substance associated with it) must control the ions' access to the channel. When the membrane potential nears the resting value, these charged particles are in a state that favors closed channels; when the membrane is depolarized, these charged particles take up a new state that favors opening of the channel. In the scheme shown in Figure 6.8, for example, the charged particles are assumed to have a positive charge. In the presence of a large, inside-negative electric field across the

Figure 6.8
A schematic representation of the voltage-sensitive gating of a membrane ion channel. In this model, the conducting state of the channel is assumed to depend on the binding of a charged particle to a site on the outer face of the membrane.



membrane, most of these particles would likely gather near the inner face of the membrane. Upon depolarization, however, the distribution of charged particles within the membrane would even out, and the fraction of particles on the outside would increase. The channel protein in Figure 6.8 is assumed to have a binding site on the outer edge of the membrane that controls the conformation of the "gating" portion of the channel. When the binding site is unoccupied, the channel is closed; when the site binds a positively charged particle (called a **gating particle**), the channel opens. Thus, upon depolarization, the fraction of channels with a gating particle on the binding site will increase, as will the total ionic conductance of the membrane.

We must emphasize that the drawings in Figure 6.8 are meant for illustrative purposes only. It is not clear, for example, that the gating particles are positively charged, although evidence from molecular studies suggests they are. Negatively charged particles moving in the opposite direction or a dipole rotating in the membrane could accomplish the same voltage-dependent gating function. Although the molecular mechanism underlying the change in the conducting state of the channel protein is unknown, a conformation change related to the charge distribution within the membrane is suspected to be involved.

The **S**-shaped relationship between ionic conductance and membrane potential (see Fig. 6.7) is expected from basic physical principles that govern the movement of charged particles under the influence of an electric field (diagrammed schematically in Figure 6.8). The distribution of charged particles within the membrane will be related to the transmembrane electric field (that is, the membrane potential) according to the Boltzmann relation:

$$P_o = \frac{1}{1 + e^{\left(\frac{W - z\epsilon E_m}{kT}\right)}} \tag{6.3}$$

where P_o is the proportion of positive gating particles on the outside of the membrane, z is the valence of the gating charge, ϵ is the electronic charge, E_m is the membrane potential, k is Boltzmann's constant, T is the absolute temperature, and W is a voltage-independent term giving the offset of the relation along the voltage axis. The steepness of the rise in P_o with depolarization depends on the valence, z, of the gating charge; the larger z becomes, the steeper the rise of P_o (and conductance) with depolarization. As noted earlier, the sodium and potassium conductances are strongly dependent on membrane potential, implying that the gating charge that opens a channel has a large valence. For example, to produce a rise in sodium conductance like that observed experimentally, the effective valence of the gating particle must be approximately 6 [that is, $z \approx 6$ in Equation (6.3)].

Kinetics of the change in ionic conductance following a step depolarization

In chapter 5, we saw that differences in the speed with which the three types of voltage-sensitive gates respond to voltage changes help determine the form of the action potential. For instance, the opening of the potassium channels must be delayed with respect to the opening of the sodium channels to avoid wasteful competition between sodium influx and potassium efflux during the depolarizing phase of the action potential. We will now consider how the time-course, or kinetics, of the conductance changes fit into the charged gating particle scheme.

Hodgkin and Huxley assumed that the rate of change in the membrane conductance to an ion following a step depolarization was governed by the rate of redistribution of the gating particles within the membrane. That is, they assumed that the interaction between gating particle and binding site introduced a negligible delay into the temporal behavior of the channel. As an example, we will consider the kinetics involved in the opening of the sodium channel following a step depolarization. In formal terms, the movement of gating particles within the membrane can be described by the following first-order kinetic model:

$$m \underset{b_m}{\overset{a_m}{\leftrightarrows}} (1 - m) \tag{6.4}$$

In this equation, m is the proportion of particles on the outside of the membrane, where they can interact with the binding sites, and $1 - m$ is the proportion of particles on the inside of the membrane. The rate constant, a_m, represents the rate at which particles move from the inner face of the membrane to its outer face, and b_m is the rate of reverse movement. Because the particles are charged, a step change in the membrane voltage will bring an instantaneous change in a_m and b_m. For instance, a step depolarization would increase a_m and decrease b_m, leading to a net increase in m and a corresponding decrease in $1 - m$.

The equation governing the rate at which the charges are redistributed following a change in membrane potential is

$$dm / dt = a_m (1 - m) - b_m m \tag{6.5}$$

In Equation (6.5), dm/dt is the net rate of change of the proportion of particles on the outside face of the membrane. In other words, $a_m(1 - m)$ is the rate at which particles are leaving the inside of the membrane, and $b_m m$ is the rate at which particles are leaving the outside surface; the difference between those two rates gives the net rate of change in m. If the distribution of particles is stable—for example, if E_m has been constant for a long time—particles will move from the inside of the membrane to the outside at the same rate that they move in the opposite direction, and dm/dt will be zero. If the system is suddenly perturbed by a depolarization, a and b will change, destroying the balance on the right side of Equation (6.5). If the depolarization is maintained, the rate at which the system will approach a new steady distribution of particles will be governed by Equation (6.5).

The solution of a first-order kinetic expression like Equation (6.5) is an exponential function; that is, following a step change in membrane voltage, m will approach a new steady value exponentially. The exponential solution can be written as

$$m(t) = m_\infty - (m_\infty - m_0)e^{-(a_m + b_m)t} \tag{6.6}$$

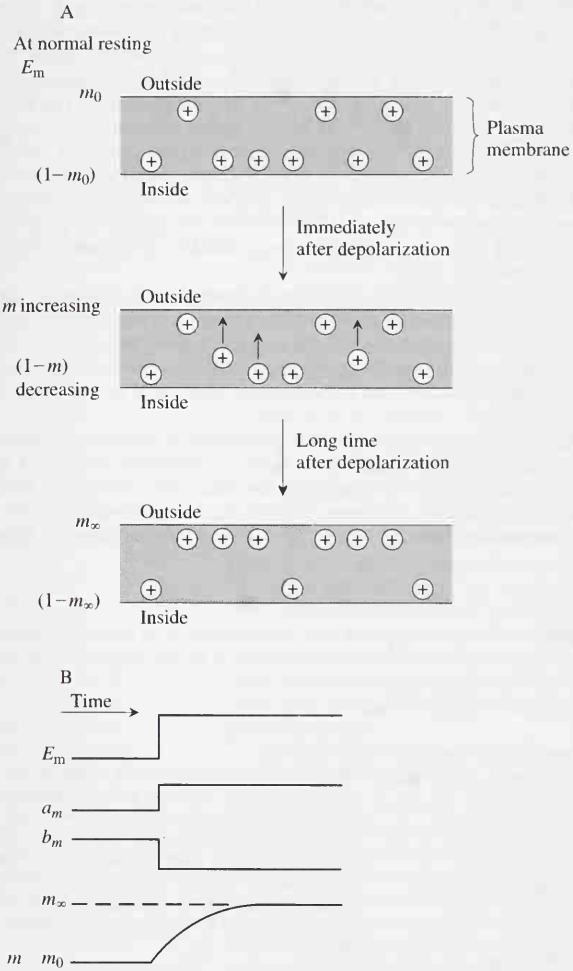
According to Equation (6.6), following a change in membrane potential, m will change exponentially from its initial value (m_0) to its final value (m_A) at a rate governed by the rate constants (a_m and b_m) for movement of the gating particles at that new value of membrane potential.

The behavior of m with time after a depolarization, as expected from Equation (6.6), is summarized in Figure 6.9. The number of binding sites occupied by gating particles is proportional to m, which represents the fraction of available particles on the outer face of the membrane. Thus, if the occupation of a single binding site causes the channel to open, and if the interval between binding of the gating particle and opening of the channel involves no significant delays, the number of open channels would be expected to follow the same exponential time-course as m after a step depolarization.

Because the total membrane sodium conductance is determined by the number of open sodium channels, sodium conductance measured with a

Figure 6.9

The change in the distribution of sodium-channel gating particles after depolarization of the membrane. (A) A schematic diagram of the distribution of charged gating particles at the normal resting potential and at different times after depolarization of the membrane. (B) The effect of a step change in the membrane potential (top trace) on the rate constants for movement of the gating particles (middle traces) and on the proportion of particles on the outer side of the membrane (bottom trace).



voltage clamp would be expected to be exponential, given the assumption that a single gating particle can cause the channel to open. Figure 6.10 illustrates this prediction and diagrams the experimentally observed kinetic behavior of g_{Na}. Unlike the predicted exponential behavior, the rise in g_{Na} actually exhibited a pronounced delay following the voltage step. The S-shaped increase in g_{Na} would be explained if more than one binding site must be occupied by gating particles before the channel can open. If the binding to each of several sites occurs independently, the probability that any one site is occupied will be proportional to m and will therefore rise exponentially with time after a step voltage change. The probability that all of a number of sites will be occupied will be the product of the probabilities that each individual site will bind a gating particle. Thus, in the case of two binding sites, the probability that both are occupied will be the product of the probability that site 1 binds a particle and the probability that site 2 binds a particle. Because each of these probabilities is proportional to m, the joint probability that both sites are occupied is proportional to m^2. Similarly, if x sites are available, the probability of channel opening would be proportional to m^x.

The actual rise in sodium conductance following a depolarization step suggested that $x = 3$ for the sodium channel. That is, three binding sites must be occupied by gating particles before the sodium channel will conduct. The rise in g_{Na} following a voltage-clamp step to a particular level of depolarization was proportional to m^3, and the temporal behavior of m was given by Equation (6.6).

A similar analysis was carried out for the change in potassium conductance following a step depolarization. The results suggested that $x = 4$ for the voltage-sensitive potassium channel of the squid axon membrane. Thus, the gating charges for the potassium channel became redistributed after a change in membrane potential according to a relation equivalent to Equation (6.5):

$$dn / dt = a_n (1 - n) - b_n n \tag{6.7}$$

By analogy with the sodium system, n is the proportion of potassium gating particles on the outside of the membrane, $1 - n$ is the proportion on the

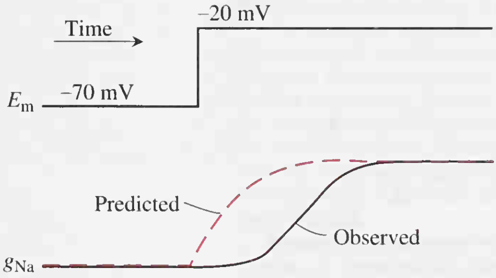


Figure 6.10
The predicted time-course of the change in sodium conductance following a depolarizing step (dashed line), assuming that the proportion of open channels—and hence the total sodium conductance—is directly related to the fraction of gating particles on the outer face of the membrane. The solid line shows the observed change in sodium conductance following a step depolarization.

inner face of the membrane, and a_n and b_n are the rate constants for particle movement from one membrane face to the other. Equation (6.7) has a solution equivalent to that for Equation (6.6):

$$n(t) = n_\infty - (n_\infty - n_0)e^{-(a_n + b_n)t} \tag{6.8}$$

In this equation, n_0 and n_A are the initial and final values of n. The rise in potassium conductance following a step depolarization was found to be proportional to n^4; therefore, the potassium channel behaves as if four binding sites must be occupied by gating particles before the gate will open. A major difference between the potassium and the sodium channels is that the rate constants, a_n and b_n, are smaller for the potassium channels. That is, the sodium-channel gating particles appear to be more mobile than their potassium-channel counterparts. As a result, the sodium channel opens more rapidly after a depolarization—a crucial part of the action potential mechanism.

Sodium inactivation

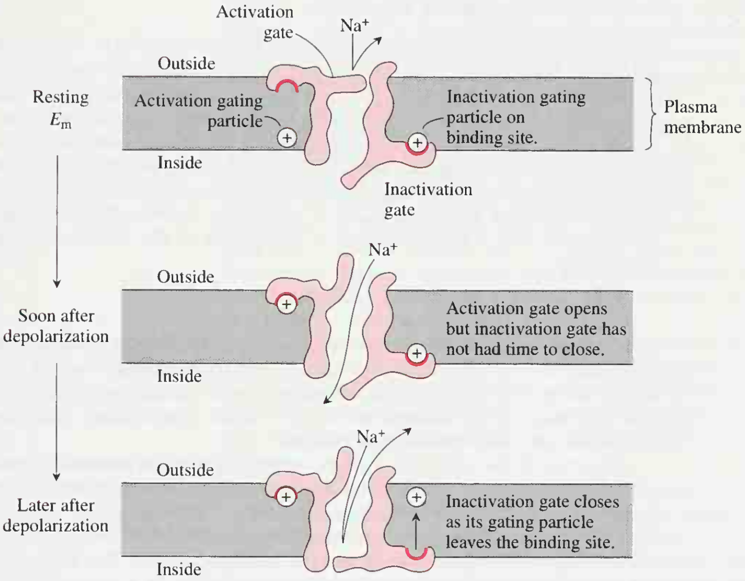
As noted earlier, the change in sodium conductance following a maintained depolarization step is transient. We have so far considered only the first part of that change: the increase in sodium conductance (sodium activation). We will now turn to the delayed decline in sodium conductance following depolarization, called sodium inactivation.

Following in the same vein used to analyze sodium and potassium channel opening, Hodgkin and Huxley assumed that sodium inactivation was caused by a voltage-sensitive gating mechanism. They supposed that the conducting state of the sodium channel was controlled by two gates: the activation gate (discussed above), and the inactivation gate (Fig. 6.11). Like the activation gate, the inactivation gate is controlled by a charged gating particle and remains open when its binding site is occupied. Unlike the activation gate, however, the inactivation gate is normally open and closes upon depolarization. If the gating particle is assumed to carry a positive charge, this behavior can be modeled by an arrangement in which the inactivation gate and its binding site lie on the inner face of the membrane. Upon depolarization, the probability that a gating particle is found on the inner face decreases, which subsequently increases the probability that the gate will close.

To study the voltage-dependence of the sodium inactivation process, Hodgkin and Huxley used a fixed depolarizing test step of a particular amplitude and measured the peak amplitude of the increase in sodium conductance that resulted from this step (Fig. 6.12). The test depolarization was preceded by a long-duration prepulse whose amplitude could be varied. They discovered that a depolarizing prepulse reduced the amplitude of the response to the test depolarization, while a hyperpolarizing prepulse increased the size of the test response (see Fig. 6.12). This finding implied that the depolarizing prepulses closed the inactivation gates of some portion of the sodium channels, preventing those channels from conducting even when the activation gates were opened by the subsequent depolarization.

Figure 6.11

A diagram of the sodium-channel protein, showing the effects of both activation and inactivation gates.

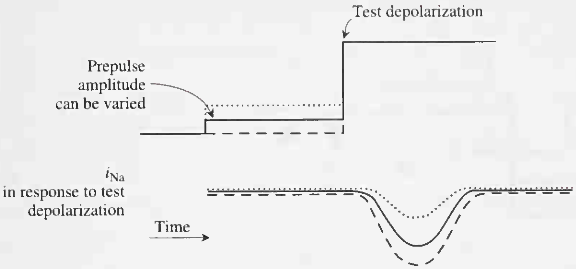

Activation gate
Na+
Outside
Resting E_m
Activation gating particle
Inactivation gating particle on binding site.
Plasma membrane
Inside
Inactivation gate
Na+
Outside
Soon after depolarization
Activation gate opens but inactivation gate has not had time to close.
Inside
Na+
Outside
Later after depolarization
Inactivation gate closes as its gating particle leaves the binding site.
Inside

As a result, a smaller increase in sodium conductance was noted during the test step.

The finding that hyperpolarizing prepulses increased the test response suggests that the inactivation gates of some portion of the sodium channels are already closed at the normal resting potential. Increasing E_m causes those gates to open, and the channels then become able to conduct in response to the test depolarization. By varying the amplitude of the prepulse, Hodgkin and Huxley were able to establish the dependence of the inactivation gate on membrane potential. Figure 6.13 illustrates the relationship between E_m during the prepulse and the peak sodium conductance during the test depolarization. In the figure, note that all inactivation gates close when the membrane potential reaches approximately 0 mV, and that even a small depolarization can generate a significant reduction in the peak change in sodium conductance.

The time-course of sodium inactivation was studied by varying the duration of the prepulse, rather than its amplitude. With short prepulses, the inactivation gates had little time to close, and the response to the test

Figure 6.12
The procedure for measuring the voltage-dependence of sodium inactivation.


Test depolarization
Prepulse amplitude can be varied
i_{Na} in response to test depolarization
Time

depolarization was only slightly reduced. With longer prepulses, a progressively larger effect was observed (Fig. 6.14). These data were described by a single exponential equation, rather than by the powers of exponentials used to describe the kinetics of sodium and potassium activation. Recall from the discussion of the voltage-dependent opening of the sodium channel that a single exponential would be expected if the gate's status were controlled by a single gating particle. Thus, the closing of the inactivation gate appears to occur when a single particle leaves a single binding site on the gating mechanism. An equation analogous to Equations (6.6) and (6.8) can be written to describe the temporal behavior of this gate:

$$h(t) = h_\infty - (h_\infty - h_0)e^{-(a_h+b_h)t} \qquad (6.9)$$

Figure 6.13
The relationship between the amplitude of an inactivating prepulse and the peak sodium conductance in response to a subsequent test depolarization.

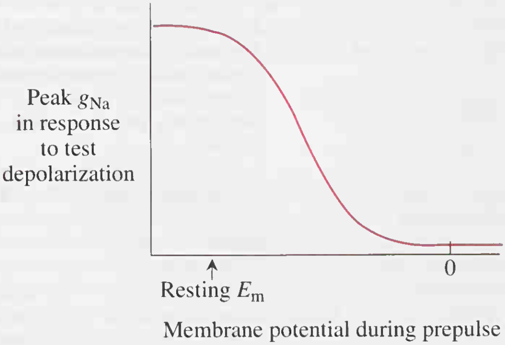
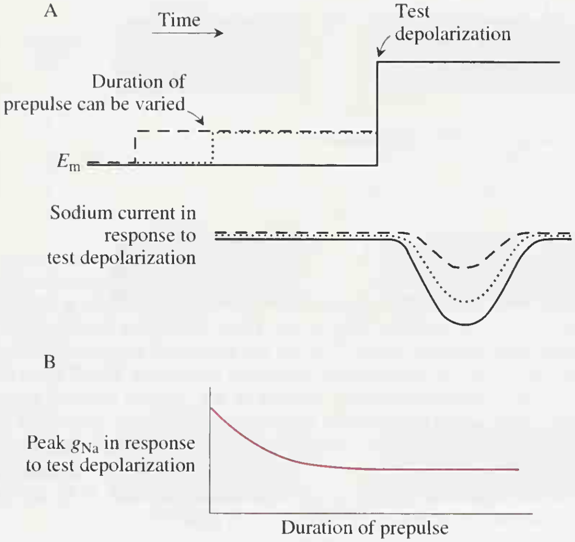


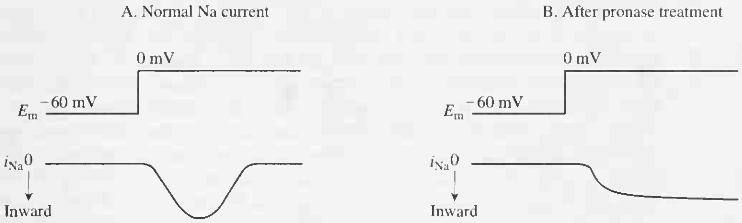
Figure 6.14
(A) The procedure for measuring the time-course of sodium inactivation by varying the duration of depolarizing prepulses. (B) The exponential time-course that results from the closing of the inactivation gate of the sodium channel.



In this case, however, h decreases with depolarization; that is, it declines exponentially from its original value (h_0) to its final value (h_A). The rate of that decline is governed by the rate constants, a_h and b_h, for movement of the inactivation gating particle through the membrane. As expected from the discussion in chapter 5, the closing of the inactivation gate occurs more slowly than the opening of the activation gate, implying that the inactivation gating particle is less mobile (and the rate constants are therefore smaller).

Is there any reason to suppose that the activation and inactivation gates are separate entities? After all, the channel might exhibit the same behavior if it possessed a single gate that first opens, then closes upon depolarization. Evidence suggests, however, that the processes of activation and inactivation of the sodium channel are controlled by distinct and separate parts of the channel protein molecule. If a proteolytic enzyme, such as trypsin or pronase, is applied to the intracellular membrane face, sodium-channel inactivation is selectively eliminated, leaving activation intact (Fig. 6.15). As we

Figure 6.15
Removal of the inactivation gate by treating the inside of the membrane with a proteolytic enzyme, pronase. (A) Normal sodium current. The current rises (activates), and then declines (inactivates) during a maintained depolarization. (B) Sodium current after pronase treatment. The current activates normally, but fails to inactivate during a maintained depolarization.



have seen previously, the sodium current normally increases, then decreases after a step depolarization as the channels open and then close with a delay (see Fig. 6.15A). After applying a protease to the internal face of the membrane (see Fig. 6.15B), the sodium current increases upon depolarization as usual, but the current continues for the duration of the depolarization. Thus, the inactivation gate has been destroyed but activation remains normal. This finding supports the idea that two separate gates control access to the sodium-channel pore. It also suggests that the inactivation gate lies on the intracellular part of the channel protein molecule, because the proteolytic enzyme proves ineffective when applied on the outside of the membrane. This finding agrees with molecular biological evidence, which also places the inactivation gate on the intracellular portion of the sodium channel (see chapter 5).

The temporal behavior of sodium and potassium conductances

To specify the time-course of the changes in sodium and potassium conductances following a depolarizing voltage-clamp step, we need know only the behavior of the gating parameters *m, n,* and *h*. In equation form, the sodium and potassium conductances would be given by

$$g_{Na} = \bar{g}_{Na} m^3 h \tag{6.10}$$

$$g_K = \bar{g}_K n^4 \tag{6.11}$$

where $\bar{g}_{Na}$ and $\bar{g}_K$ are the maximal sodium and potassium conductances, and *m, n,* and *h* are given by Equations (6.6), (6.8), and (6.9), respectively. Following a depolarization, the sodium conductance rises in proportion to the third power of the activation parameter, *m,* and falls in direct proportion to the decline in the inactivation parameter, *h*. The potassium conductance rises as the fourth power of its activation parameter and does not undergo inactivation.

The names used in chapter 5 for the various voltage-sensitive gates of the potassium and sodium channels derive from the variables chosen by Hodgkin and Huxley to represent these activation and inactivation parameters. The sodium activation gate is called the m gate, the sodium inactivation gate is known as the h gate, and the potassium gate is called the n gate, reflecting the roles of those parameters in Equations (6.10) and (6.11).

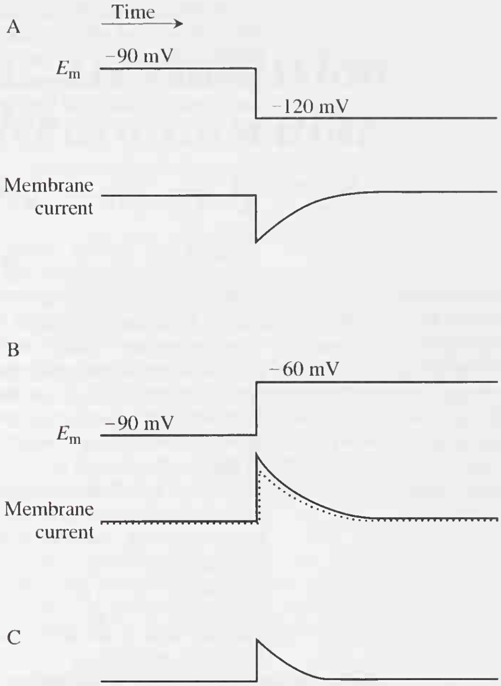
To test a theory like that related to the action potential, the best course of action is to see if it can quantitatively describe the event intended. Hodgkin and Huxley, for example, tested their theory by determining whether they could quantitatively reconstruct the action potential of a squid giant axon using the system of equations they derived from their analysis of voltage-clamp data. Because the action potential does not occur under voltage-clamp conditions, this test required knowing both the voltage-dependence and the time-dependence of a large number of parameters. To find these relationships, they needed to define how the rate constants for all three gating particles and the maximum values of h, m, and n depend on the membrane voltage. All of these parameters were determined experimentally from a complete set of voltage-clamp experiments, allowing Hodgkin and Huxley to calculate the action potential that would occur if their axon were not voltage-clamped. They then compared their calculated action potential with the action potential recorded from the same axon when the voltage-clamp apparatus was switched off. The calculated action potential reproduced the features of the real one in exquisite detail, confirming that they had covered all relevant features of the nerve membrane involved in the generation of the action potential.

Gating currents

Hodgkin and Huxley realized that their theory of the gating of the sodium and potassium channel predicted the existence of an electrical current flow within the membrane that would be associated with the movement of the charged gating particles. When a step change in membrane potential occurs, the charged gating particles are redistributed within the membrane. Because the movement of charge through space is an electrical current (by definition), this redistribution of charges from one face of the membrane to the other should be measurable as a rapid component of membrane current that responds to the voltage change. A current of this sort flowing *within* a material is called a **displacement current.**

Although the equipment available to Hodgkin and Huxley was inadequate to detect this small current, Armstrong and Bezanilla managed to measure the displacement current associated with the movement of the gating particles almost 20 years later. The procedure for measuring what are now called **gating currents** (because of their presumed function in the membrane) is illustrated in Figure 6.16. In this technique, the membrane potential is held at a hyperpolarized level, which ensures that all gating particles remain on the inner face of the membrane (assuming that the gating particles are positively charged). In addition, all sodium and potassium currents through the channels are blocked by administration of drugs, such as tetrodotoxin and tetraethylammonium. A step is then made to a more

Figure 6.16
The procedure for isolating the gating current associated with opening of voltage-sensitive sodium channels of an axon membrane. (A) Membrane voltage is stepped negative from a hyperpolarized level. With all ion channels blocked, the only current flowing is that required to move the membrane voltage in a more negative direction. (B) Membrane voltage is stepped positive from a hyperpolarized level. The current necessary to move the potential in the positive direction (dotted trace) will have the same amplitude, but the opposite sign, as in A. In addition, B will include an extra component of current caused by the movement of the charged gating particles in response to the depolarization. This component is seen in C on an expanded vertical scale.



Gating current isolated after subtracting current in (A) from that in (B).

hyperpolarized level—for example, 30 mV more negative. Because all gating charges are already on the inner face of the membrane, no displacement current will flow as the result of this hyperpolarizing step. Instead, the only current flowing will consist of the rapid influx of negative charge necessary to step the voltage. The voltage is then returned to the original hyperpolarized holding level, and a 30 mV depolarizing step is made. The influx of positive charge necessary to depolarize by 30 mV will be equal in magnitude, but opposite in sign, to the influx of negative charge necessary to make the previous 30 mV hyperpolarizing step. The depolarizing step will, however, cause some gating charges to move from the inner face of the membrane to the outer face. Thus, an extra component of current, due to the movement of gating charges, will arise in response to the depolarizing step. By subtracting the current generated in response to the hyperpolarizing step from the depolarizing current, this extra gating current can be isolated.

Experiments on this gating current suggest that it has the correct voltage-dependence and other properties to represent the charge displacement underlying the gating scheme suggested by Hodgkin and Huxley. This finding provides an important piece of evidence validating a basic feature of Hodgkin and Huxley's model of the membrane of excitable cells.

SUMMARY

Hodgkin and Huxley made the fundamental observations on which our present understanding of the ionic basis of the action potential is based. In their experiments, they measured the ionic currents flowing across the membrane of a squid giant axon in response to changes in membrane voltage. Their procedure utilized a voltage-clamp apparatus, which provides a means of holding membrane potential constant in the face of changes in the ionic conductance of the axon membrane. By analyzing these ionic currents, Hodgkin and Huxley derived equations specifying both the voltage-dependence and the time-course of changes in sodium and potassium conductance of the membrane.

During a maintained depolarization, sodium conductance increased rapidly, then declined; potassium conductance showed a delayed but maintained increase. Analysis of the change in sodium conductance suggested that the conducting state of the sodium channel was controlled by a rapidly opening activation gate, called the m gate, and a slowly closing inactivation gate, called the h gate. Both gates behave as if controlled by charged gating particles that move within the plasma membrane. When the gating particles occupy binding sites associated with the channel gating mechanism, the gates open. The kinetics of the observed gating behavior are explained by the kinetics of the redistribution of the charged gating particles within the membrane following a step change in the transmembrane potential. The sodium activation gate opens when three independent binding sites are occupied by gating particles, while the inactivation gate closes when a single particle leaves a single binding site. The potassium channel is controlled by a single gate, the n gate, that opens when four binding sites are occupied.

The rate at which the gating particles are redistributed after a depolarization differs for the three types of gates, with sodium activation gating occurring more rapidly than sodium inactivation or potassium activation. Tiny membrane currents associated with the movement of the charged gating particles within the membrane have been detected.

7

Synaptic Transmission at the Neuromuscular Junction

Chapter 5 was concerned with the ionic basis of the action potential, the electrical signal that carries messages long distances along nerve fibers. Using the patellar reflex as an example, we discussed the mechanism that allows a message, "the muscle was stretched," to travel along the membrane of the sensory neuron from the sensory endings in the muscle to the termination of the sensory fiber in the spinal cord. This chapter will focus on the mechanism by which activity in the motor neuron is passed along to the cells of the muscle, causing the muscle cells to contract. Chapter 8 will then consider how action potentials in the sensory neuron influence motor neuron activity.

CHEMICAL AND ELECTRICAL SYNAPSES

The point at which activity is transmitted from one nerve cell to another, or from a motor neuron to a muscle cell, is called a **synapse.** The patellar reflex includes two synapses: one between the sensory neuron and the motor neuron in the spinal cord, and one between the motor neuron and the cells of the quadriceps muscle. Synapses are classified into two general groups: electrical synapses and chemical synapses. Both types are characterized by specialized membrane structures at the point where the input cell, called the **presynaptic cell,** comes into contact with the output cell, called the **postsynaptic cell.**

At a chemical synapse, an action potential in the presynaptic cell causes it to release a chemical substance (called a **neurotransmitter**), which diffuses through the extracellular space and changes the membrane potential of the postsynaptic cell. At an electrical synapse, a portion of the change in membrane potential (such as the depolarization during an action potential) in the presynaptic cell spreads directly to the postsynaptic cell without the intervention of an intermediary chemical. Both synapses in the patellar reflex—and indeed most synapses in mammalian nervous systems—consist of chemical synapses.

At chemical synapses, the membranes of the presynaptic and postsynaptic cells come close to each other but are still separated by a small gap of extracellular space. At an electrical synapse, the presynaptic and postsynaptic membranes touch and the cell interiors are directly interconnected by means of special ion channels called gap junctions, which allow flow of electrical current from one cell to the other. This chapter will focus on chemical synaptic transmission. Electrical synaptic transmission will be described in more detail in chapter 13.

The neuromuscular junction as a model chemical synapse

The best-understood chemical synapse is that found between a motor neuron and a muscle cell, which is called the **neuromuscular junction** (or the **myoneural junction**). Although the finer details may differ somewhat, the basic scheme that describes the functioning of the neuromuscular junction appears to apply to all chemical synapses. Consequently, this chapter will concentrate on the characteristics of this special synapse at the end of the patellar reflex. In the next chapter, we will consider some of the differences between the synapse at the neuromuscular junction and synapses in the central nervous system, such as that between the sensory and motor neurons in the spinal cord.

TRANSMISSION AT A CHEMICAL SYNAPSE

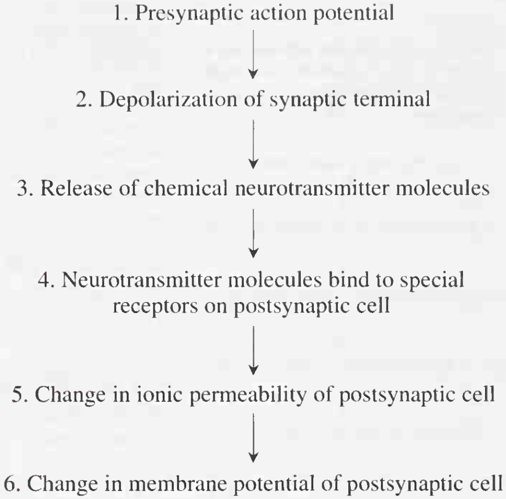
Figure 7.1 summarizes the sequence of events that occurs during neuromuscular synaptic transmission. When an action potential arrives at the end of the motor neuron nerve fiber, it invades a specialized structure called the **synaptic terminal.** Depolarization of the synaptic terminal induces the release of a chemical messenger, which is stored inside the terminal. At the vertebrate neuromuscular junction, this chemical messenger is **acetylcholine** (Fig. 7.2). Acetylcholine (abbreviated ACh) diffuses across the space separating the presynaptic motor neuron terminal from the postsynaptic muscle cell and alters the ionic permeability of the muscle cell membrane. This change produces a depolarization of the muscle cell membrane. The remainder of this chapter will provide a detailed description of this basic sequence of events.

Presynaptic action potential and acetylcholine release

The occurrence of an action potential in the synaptic terminal triggers the ACh release. The depolarization during the action potential is the stimulus for transmitter release; thus, any experimental manipulation that depolarizes the synaptic terminal causes ACh to be released. This coupling between depolarization and ACh release is not direct, however. Instead, the coupling is mediated by the influx into the synaptic terminal of a type of ion in the ECF that we have largely ignored to this point—calcium ions.

Calcium is present at a low concentration in ECF and is not an important factor for the resting membrane potential or for most nerve action potentials (although some neuronal action potentials have a contribution from calcium influx, as described in chapter 5). However, the release of a chemical neurotransmitter at a synapse requires calcium ions in the ECF. If calcium ions are

Figure 7.1
The sequence of events during transmission at a chemical synapse.

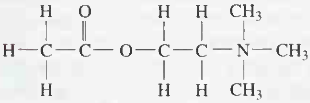

1. Presynaptic action potential
2. Depolarization of synaptic terminal
3. Release of chemical neurotransmitter molecules
4. Neurotransmitter molecules bind to special receptors on postsynaptic cell
5. Change in ionic permeability of postsynaptic cell
6. Change in membrane potential of postsynaptic cell

removed from the ECF, depolarization of the synaptic terminal can no longer induce release of ACh. Depolarization causes external calcium ions to enter the synaptic terminal, and the calcium subsequently causes ACh to be released from the terminal.

What mechanism links the depolarization of the terminal to the influx of calcium ions? As we've seen in earlier chapters, ions cross membranes through specialized transmembrane channels. Calcium ions do not deviate from this pattern. The membrane of the synaptic terminal contains calcium channels that remain closed as long as E_m is near its normal resting level. These channels behave similarly to the voltage-dependent potassium channels of nerve membrane; that is, they open upon depolarization and close again when the membrane potential repolarizes. Thus, when an action potential invades the synaptic terminal, the calcium permeability of the membrane increases during the depolarizing phase of the action potential and declines when membrane potential returns to normal levels.

While the external calcium concentration is small (1–2 mM), the internal concentration of calcium ions that are free to diffuse across the plasma membrane is even smaller ($<10^{-6}$ M). From the Nernst equation, the equilibrium potential for calcium would be expected to be positive. Therefore, both the concentration and electrical gradients for calcium drive these ions into the terminal, and an increase in calcium permeability is accompanied by an influx of calcium. During a presynaptic action potential, a spike

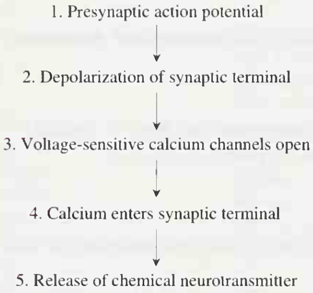
Figure 7.2
The chemical structure of acetylcholine, the chemical neurotransmitter at the neuromuscular junction.



$$H_3C{-}C({=}O){-}O{-}CH_2{-}CH_2{-}N(CH_3)_3$$

of calcium entry into the terminal occurs, resulting in the release of neurotransmitter into the extracellular space. This sequence is summarized in Figure 7.3.

Figure 7.3
The sequence of events between the arrival of an action potential at a synaptic terminal and the release of a chemical transmitter.


1. Presynaptic action potential
2. Depolarization of synaptic terminal
3. Voltage-sensitive calcium channels open
4. Calcium enters synaptic terminal
5. Release of chemical neurotransmitter

Effect of ACh on the muscle cell

The goal of synaptic transmission at the neuromuscular junction is contraction of the muscle cell. Acetylcholine released from the synaptic terminal accomplishes this goal by depolarizing the muscle cell. Because muscle cells are excitable cells (like neurons), a depolarization that exceeds the threshold level initiates an all-or-nothing, propagating action potential. The coupling between the muscle action potential and contraction will be discussed in chapter 9. This section will discuss the effect of ACh on the muscle cell membrane.

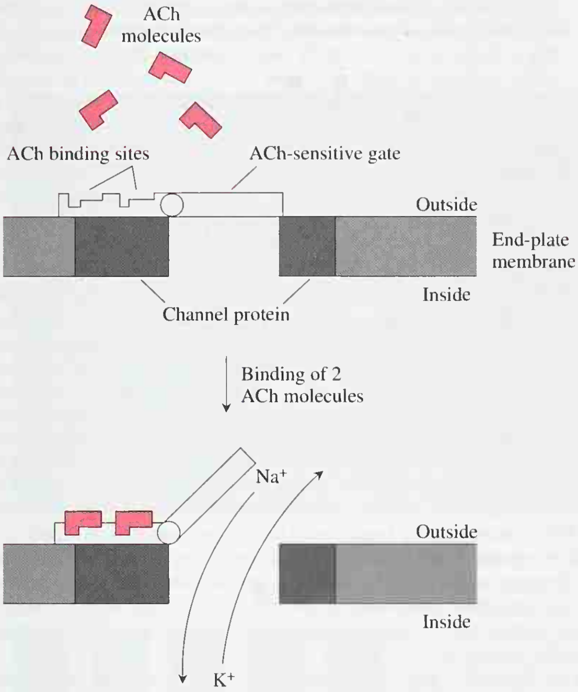
The region of muscle membrane where synaptic contact occurs is called the **end-plate** region, and it possesses special characteristics. In particular, the end-plate membrane is rich in a transmembrane protein that acts as an ion channel. Unlike the voltage-dependent channels discussed in chapter 5, however, this channel is little affected by membrane potential. Instead, this channel is sensitive to ACh: it opens when it binds acetylcholine. ACh released from the synaptic terminal diffuses across the synaptic cleft to the muscle membrane, where it combines with specific receptors associated with the ion channel. The gate on the channel remains closed when ACh is absent (Fig. 7.4). When the receptor sites are occupied, however, the protein undergoes a conformational change, the gate opens, and the channel permits ions to move across the membrane. Current evidence indicates that two ACh molecules must bind to the channel before the gate will open. The ACh-binding site is highly specific, and only ACh or a small number of structurally related compounds can bind to the site and cause the channel to open.

The ACh-activated channel of the muscle end-plate permits both sodium and potassium to cross the membrane equally well. Thus, when ACh is present, the membrane permeability to both sodium and potassium increases. How can such a permeability increase produce a depolarization of the muscle cell? Recall from chapter 4 that membrane potential depends on the relative sodium and potassium permeabilities of the membrane (the Goldman equation). For the cell of Figure 7.5, for example, p_{Na}/p_K is 0.02 at rest and E_m would be approximately −71 mV, assuming typical ECF and ICF (see Table 3.1). In the presence of ACh, however, p_{Na} and p_K increase by equal amounts, p_{Na}/p_K increases to 0.51, and E_m depolarizes to approximately −17 mV.

In a muscle cell, a somewhat more complicated situation than that seen in Figure 7.5 prevails because the ACh-activated channels are spatially restricted to the end-plate region. Thus, the permeability increase occurs in only part of the cell membrane. In this case, the result would be quantitatively different from, but qualitatively similar to, the example in Figure 7.5.

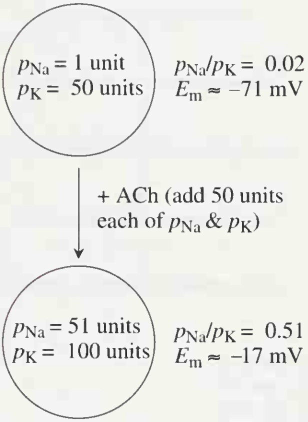
The ACh-activated channels are packed densely in the muscle end-plate region, providing a good opportunity to visualize the protein molecules that form the channel. Because the protein molecules are very small, however,

Figure 7.4
A schematic representation of the behavior of the acetylcholine-sensitive channel in the end-plate membrane. The binding of two ACh molecules to sites on the channel opens the gate, allowing sodium and potassium ions to flow through the channel.



the ACh-receptor and its channel can be discerned only at high power under the electron microscope. In the postsynaptic membrane shown in Figure 7.6, the membrane is studded with ring-shaped particles that are found only at the region of synaptic contact. These particles have been isolated from the postsynaptic membrane and chemically identified as the ACh-binding receptor molecule and its associated channel. The hole in the middle probably represents the aqueous pore through which the sodium and potassium ions cross the membrane. The ACh-activated channels have been chemically isolated from muscle membrane and can be inserted into artificial membranes (see Fig. 7.6B). Biochemical and molecular biological analysis of the

Figure 7.5
Opening a channel that allows both potassium and sodium to cross the membrane results in a higher value for p_{Na}/p_K and causes depolarization.



structure of the channel protein is well under way, and the molecular basis of its functioning will likely be understood soon.

Neurotransmitter release

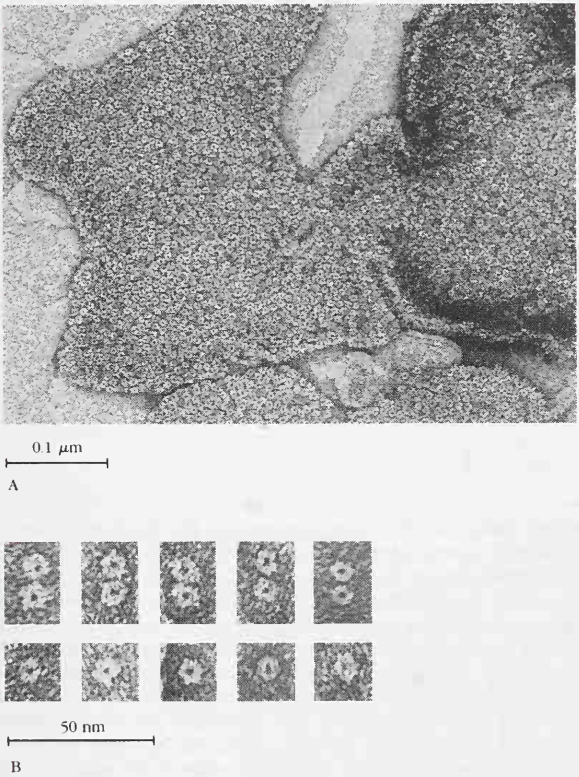
We will now return to the synaptic terminal for a more detailed examination of the mechanism of neurotransmitter release. Acetylcholine is released from the motor nerve terminal in quanta consisting of many molecules. Thus, the basic unit of release is not a single molecule of ACh, but a quantum. At the neuromuscular junction, a single quantum of ACh contains an estimated 10,000 molecules. An individual quantum is either released as a whole or not released at all. The expulsion of ACh during neuromuscular transmission can be envisioned as the sudden appearance of a "puff" of ACh molecules in the extracellular space, appearing when the entire contents of a quantum is freed. A single presynaptic action potential normally causes the release of more than 100 quanta from the synaptic terminal.

The original suggestion that ACh is released in multimolecular quanta was based on a statistical analysis of the response of the postsynaptic muscle cell to action potentials in the presynaptic motor neuron. This analysis, which was first carried out by P. Fatt and B. Katz, initiated a series of studies by Katz and co-workers that gave rise to the basic scheme for chemical neurotransmission presented here. Experimentally, the extracellular calcium concentration was reduced to the point where the influx of calcium ions into the synaptic terminal during an action potential was much lower than usual. Under these conditions, a single presynaptic action potential released on average only one or two quanta of ACh instead of the usual 100 or more quanta. Examples of end-plate potentials recorded in a muscle cell in response to a series of presynaptic action potentials are shown in Figure 7.7. Because only a small number of quanta are released for each action potential, the end-plate potentials in the reduced calcium ECF are much smaller than normal and do not reach the threshold for generating an action potential in the muscle cell.

Notice in Figure 7.7 that the amplitude of the depolarization of the muscle cell fluctuates considerably over the series of presynaptic action potentials; sometimes there was a large response and other times there was no response at all. Fatt and Katz measured a large number of such responses and found that the amplitudes clustered around particular values that represented integral multiples of the smallest observed response. For example, a cluster of responses might appear at 1 mV in amplitude, a second cluster might emerge at 2 mV, and a third cluster might arise at 3 mV (see Fig. 7.7B). This distribution indicates that the response was quantized in irreducible units of 1 mV, and that the presynaptic action potential released ACh in corresponding quantal units. Thus, a given presynaptic action potential might release three, two, one, or no quanta, but not 0.5 or 1.5 quanta.

Fatt and Katz also observed that occasional, small depolarizations occurred in the absence of any presynaptic action potential. These spontaneous

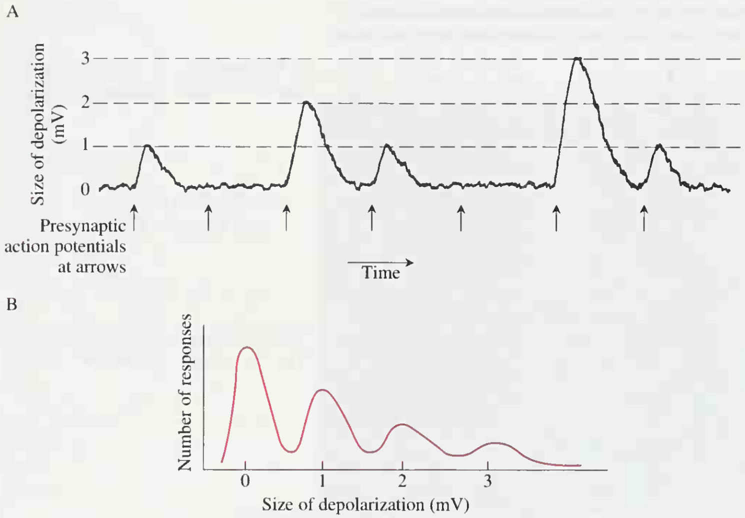
Figure 7.6
(A) A view through the electron microscope at the face of the postsynaptic membrane of the electric organ of the electric skate, *Torpedo.* This organ, which represents a rich source of acetylcholine receptors for biochemical study, is a specialized type of muscle tissue. The membrane particles are the acetylcholine-activated channels of the postsynaptic membrane. (B) Several views of individual acetylcholine receptors that have been chemically isolated from preparations like that in A, then placed in artificial membranes.



Courtesy of J. Cartaud of the Institut Jacques Monod, CNRS/Université Paris 7, France.

Figure 7.7

Quantized responses of muscle cell to action potentials in the presynaptic motor neuron. Arrows give timing of the presynaptic action potentials. The graph in B shows the peak response amplitudes that might be recorded in response to a series of several hundred presynaptic action potentials, like those seen in A.



depolarizations always had the same amplitude as the single-quantum response produced by a presynaptic action potential in low-calcium ECF. That is, if the irreducible unit of evoked muscle response was 1 mV, then the spontaneous events also had an amplitude of 1 mV. Figure 7.8 shows several spontaneous depolarizations recorded inside a muscle cell. These events, called miniature end-plate potentials, are assumed to result from spontaneous release of single quanta of ACh from the synaptic terminal. Under normal conditions, these spontaneous events occur at a low rate—about one or two per second. Any manipulation that depolarizes the nerve terminal increases their rate of occurrence, however, confirming that they are generated by the process that couples depolarization to quantal ACh release during the normal functioning of the nerve terminal.

The vesicle hypothesis of quantal transmitter release

To understand the basis of the packaging of ACh in quanta, we must examine the structure of the synaptic terminal, shown schematically in

Figure 7.8
Spontaneous miniature end-plate potentials recorded from the end-plate region of a muscle cell. These randomly occurring, small depolarizations of the muscle cell are generated by spontaneous release of single quanta of acetylcholine from the synaptic terminal of the motor neuron. (A) Four 5-s samples of muscle cell E_m, measured via an intracellular microelectrode. The spontaneous depolarizations occur at a rate of approximately one per second. (B) Spontaneous miniature end-plate potentials viewed on an expanded time scale to show the shape of the events more clearly.

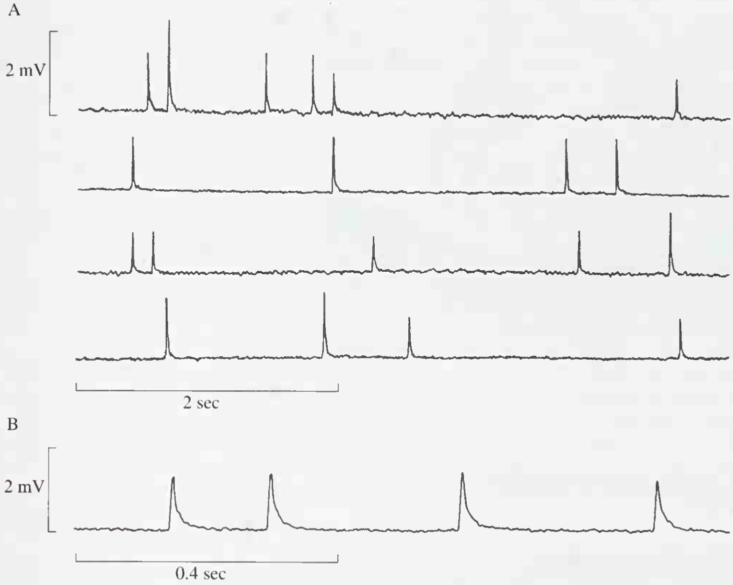


Figure 7.9. The terminal includes a large number of tiny, membrane-bound structures called **synaptic vesicles**, which contain ACh. These vesicles represent the packets of ACh that are released in response to a presynaptic action potential. It is now generally accepted that ACh release occurs when the vesicle membrane fuses with the plasma membrane of the terminal, dumping the vesicle contents into the extracellular space between the terminal and the muscle cell, as shown in Figure 7.9. The vesicles do not fuse with the plasma membrane indiscriminately. Instead, they apparently fuse only at specialized membrane regions, called **release sites** or **active zones**, that are found on the membrane face opposite the postsynaptic muscle cell. Thus, quanta of ACh are released only into the narrow space, the **synaptic cleft**, separating the presynaptic and postsynaptic cells.

Figure 7.9
The structure of the region of synaptic contact at the neuromuscular junction.

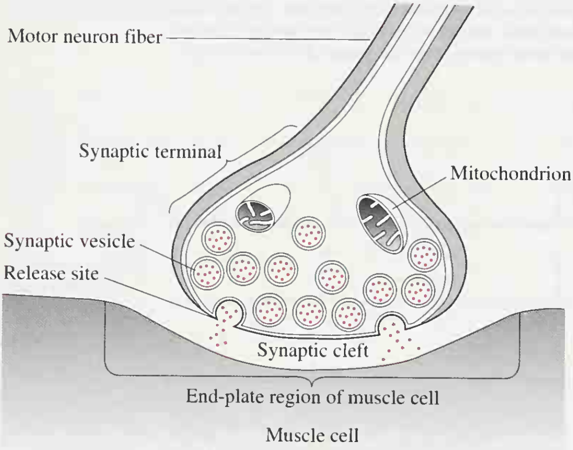


Figure 7.10
A close-up view of the synaptic region during release of acetylcholine at the neuromuscular junction.

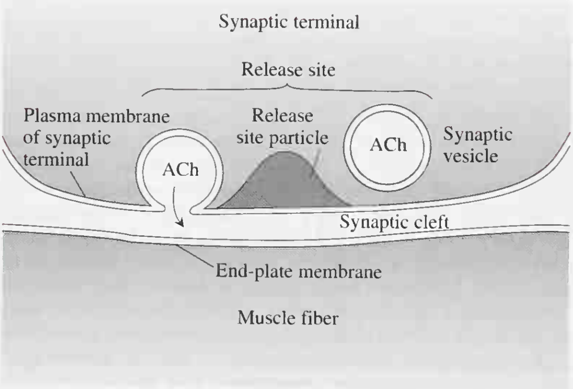


Figure 7.10 shows a close-up, schematic view of the fusion of a synaptic vesicle with the plasma membrane. With freeze-fracture electron microscopy, the active zone of the presynaptic terminal appears as a double row of large membrane particles (Fig. 7.11); these particles probably consist of membrane proteins involved in the fusion of the membrane of the synaptic vesicle and the presynaptic plasma membrane.

Elegant evidence for vesicle fusion as the mechanism of ACh release was provided by anatomical experiments by Heuser, Reese, and colleagues. In these experiments, a muscle and its attached nerve were placed in an apparatus that could very rapidly freeze the nerve and muscle. Heuser and his co-workers then literally froze the release process at the instant that an action potential arrived in the synaptic terminal. When they examined the frozen tissue in the electron microscope, using the freeze-fracture technique discussed in chapter 1, they saw synaptic vesicles in the process of fusing with the plasma membrane (see Fig. 7.11). The fusing vesicles appeared as ice-filled pits or depressions in the presynaptic membrane, lined up along the presynaptic release sites. Fusion was observed only when ACh release should have been occurring—not before or after the action potential in the terminal. Further, the fusion occurred only when calcium was present in the ECF, which we have seen is a prerequisite for release.

One of the great remaining mysteries in the mechanism of synaptic transmission is the linkage between calcium entry and vesicle fusion. No one knows how an increase in internal calcium increases the probability that a vesicle will fuse with the plasma membrane of the synaptic terminal. Calcium-binding molecules are likely associated with the release sites and with the vesicle membrane, and binding of calcium probably alters these molecular interactions in some way. The rows of membrane particles seen in freeze-fracture views of the presynaptic release sites (see Fig. 7.11) may correspond to these molecules that regulate the interaction between the vesicles and the presynaptic membrane. The molecular mechanism remains unknown, however.

Recycling of vesicle membrane

If the membranes of synaptic vesicles fuse with the plasma membrane of the terminal during transmitter release, we might expect the area of the terminal membrane to increase with use. Indeed, over the lifespan of an animal, millions of synaptic vesicles might fuse with the terminal membrane, so that the terminal might become huge. This growth does not occur, however, because the vesicle membrane does not remain part of the plasma membrane. Instead, the fused vesicles are recycled, as summarized in Figure 7.12. After fusion, the vesicles pinch off again from the plasma membrane, become refilled with ACh, and are used again to release neurotransmitter into the synaptic cleft.

Inactivation of released acetylcholine

As we saw earlier, ACh is released from the synaptic terminal and depolarizes the postsynaptic muscle cell. How is the action of ACh terminated to allow

Figure 7.11

Electron micrographs of the freeze-fractured face of a presynaptic terminal at the neuromuscular junction. (A) An unstimulated nerve terminal. Note the double row of particles defining a presynaptic release site or active zone (az). The arrow points to what appears to be a synaptic vesicle spontaneously fusing with the presynaptic membrane. Such spontaneous fusions presumably underlie the spontaneous miniature end-plate potentials shown in Figure 7.8. (B) A higher-power view of an active zone of a nerve terminal frozen during acetylcholine release stimulated by presynaptic action potentials. The depressions arrayed along either side of the active zone correspond to regions where synaptic vesicles are fusing with the presynaptic membrane.

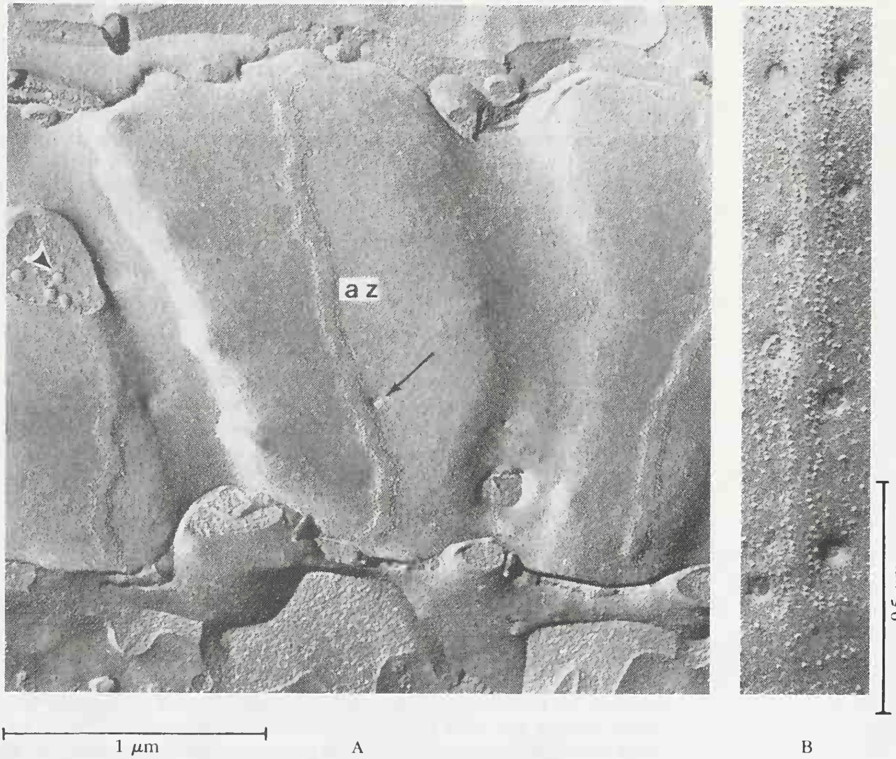


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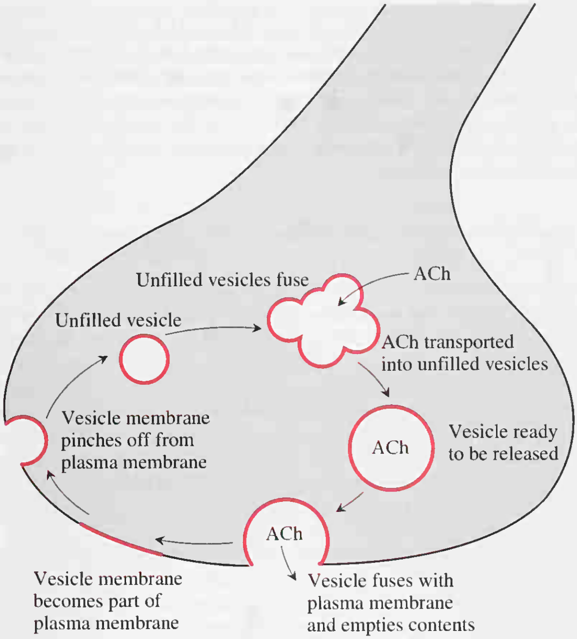
Figure 7.12
The recycling of vesicle membrane in the presynaptic terminal at the neuromuscular junction. The vesicle membrane appears in red, and the plasma membrane is black.



the end-plate region to return to its resting state? The answer involves another specialized ACh-binding protein in the end-plate region, called acetylcholinesterase. This enzyme splits ACh into acetate and choline. Because neither acetate nor choline can bind to and activate the ACh-activated channel, acetylcholinesterase effectively halts the action of any ACh it encounters.

When a puff of ACh appears in response to an action potential in the synaptic terminal, the concentration of ACh in the synaptic cleft abruptly rises. Some of the released ACh molecules bind to ACh-activated channels, causing them to open and increasing the sodium and potassium permeability of the end-plate membrane. Other ACh molecules bind to acetylcholinesterase and become inactivated. Although the binding of ACh to the postsynaptic channel is highly specific, the binding is readily reversible and typically lasts for only 1 ms. When an ACh molecule is released from a channel, the channel closes. The newly freed ACh molecule may then bind again to an ACh-activated channel, or it may bind to acetylcholinesterase and become inactivated. Over time, the concentration of ACh in the cleft will fall until all of the released ACh has been split into acetate and choline.

It would be wasteful if the choline resulting from ACh inactivation were lost and had to be replaced with fresh choline from inside the presynaptic cell. In reality, most of the choline returns to the synaptic terminal, where it is reassembled into ACh by the enzyme choline acetyltransferase. Thus, both the vesicle membrane (the packaging material of the quantum) and the released neurotransmitter (the contents of the quantum) are effectively recycled by the presynaptic terminal.

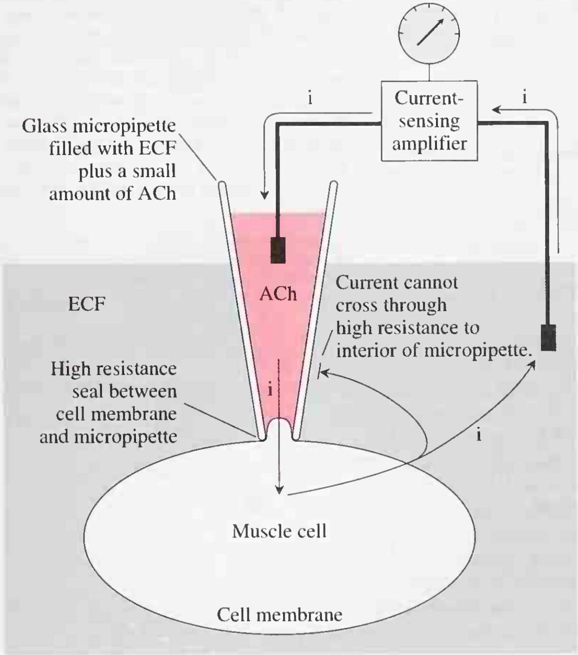
Recording the electrical current flowing through a single acetylcholine-activated ion channel

Throughout our discussion of the membrane properties of excitable cells, we have seen that ions cross the membrane through specific pores or channels. For example, the effect of acetylcholine on the muscle membrane is mediated via ion channels in the postsynaptic membrane that open in the presence of acetylcholine. As discussed in chapters 4 and 6, the flow of ions across the cell membrane constitutes a transmembrane electrical current that can be measured with electrical techniques like the voltage clamp. Recently, a new technique was developed by Neher and Sakmann to record transmembrane ionic currents. This technique, which is called the **patch clamp** (Fig. 7.13), has sufficient resolution to measure the minute electrical current flowing through a single open ion channel.

The basic idea behind the patch clamp involves the electrical isolation of a small patch of cell membrane that contains only a few ion channels. A specially constructed miniature glass pipette is placed in close contact with the membrane, so that a tight seal forms between the membrane and the glass. When one of the ion channels in the isolated patch opens, electrical current flows across the membrane. In the case of the acetylcholine-activated channel, for example, the net current would be inward (that is, depolarizing) under normal conditions. From the basic properties of electricity, we know that current must flow in a complete circuit. In the patch-clamp technique, the return current path through the extracellular space is broken by the presence of the glass pipette (see Fig. 7.13). As a result, the seal between the cell membrane and the pipette imposes a high electrical resistance. Under these conditions, the ionic current through the open channel must complete its circuit through the current-sensing amplifier connected to the interior of the pipette.

If the patch-clamp technique is to achieve sufficient sensitivity to measure the current through a single channel, the electrical resistance between the interior of the patch pipette and the extracellular space must exceed 10^9 ohms, which is a very large resistance. Fortunately for neurophysiologists, it is possible to achieve resistances greater than 10^{10} ohms.

Figure 7.13
A schematic illustration of the procedure for recording the current through a single acetylcholine-activated channel in a cell membrane. A micropipette with a tip diameter of 1 to 2 μm is placed on the membrane's external surface. The glass of the micropipette seals tightly to the membrane so that a resistance greater than 10^{10} ohms is imposed in the extracellular path for current flow through the channel. When a channel in the patch of membrane inside the micropipette opens, a current-sensing amplifier connected to the interior of the pipette detects the minute current flow.



Current-sensing amplifier
i
i
Glass micropipette filled with ECF plus a small amount of ACh
ECF
ACh
Current cannot cross through high resistance to interior of micropipette.
High resistance seal between cell membrane and micropipette
i
i
Muscle cell
Cell membrane

Using the patch clamp, the current through acetylcholine-activated channels of the postsynaptic membrane of muscle cells can be recorded by placing a small amount of acetylcholine (or structurally related compounds that are recognized by the receptors on the channel) inside the patch pipette. When these receptors are occupied, the gate opens and the channel allows ions to cross the membrane (see Fig. 7.4). In that case, we expect to record an electrical current like that shown in Figure 7.14A when the channel opens. A rapid step of inward current would arise as the gate opens, the current

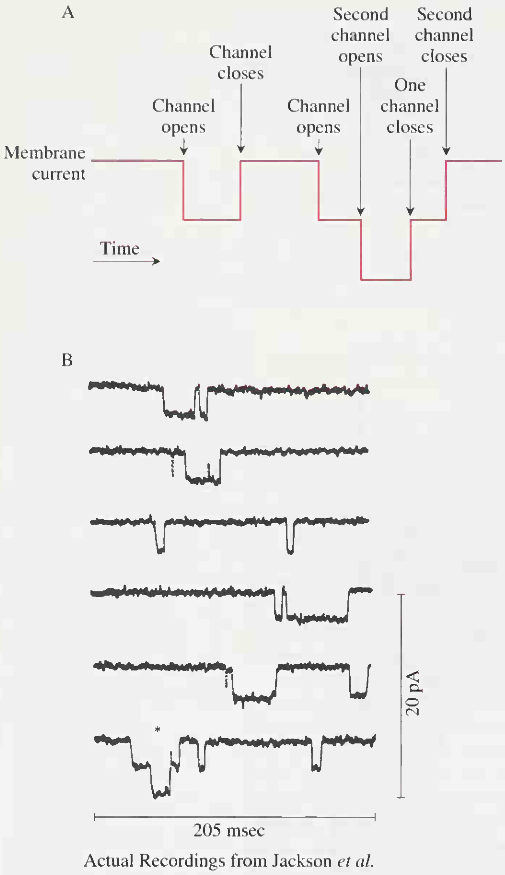


Figure 7.14
(A) The current expected to flow through a single acetylcholine-activated channel if the conducting state of the channel is controlled by a single gate that is either completely open or completely closed. When ACh binds to the gating portion of the channel, the channel opens and a stepwise pulse of inward current flows through the channel. When ACh unbinds, the channel closes and the current abruptly disappears. (B) Actual recordings of currents flowing through single acetylcholine-activated channels of human muscle cells maintained in cell culture. At the point indicated by the asterisk, two channels opened simultaneously and their currents added independently. These recordings show the fundamental postsynaptic events that underlie the interaction between the nervous system and the muscles in the human body.

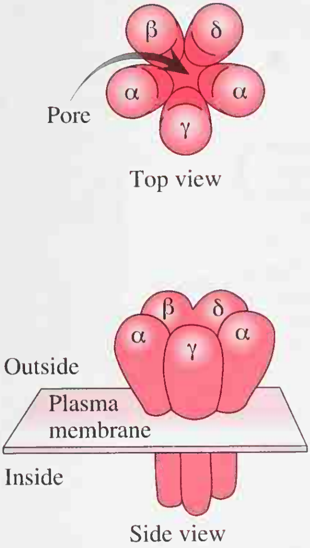
(B) Reproduced with permission from Jackson MB, Lecar H, Askanas V, Engel WK. Single cholinergic receptor channel currents in cultured human muscle. J Neurosci 1982;2:1465–1473.

would be maintained at a constant level as long as the channel remains open, and the step would terminate when acetylcholine unbinds from one of the receptor sites, causing the gate to close. If a second channel opens while the first is still open, the two currents simply add to produce a current twice as large as the single-channel current (see Fig. 7.14A).

Actual patch-clamp recordings of currents through single acetylcholine-activated channels of human muscle cells (Fig. 7.14B) show that the currents through the channels are the rectangular events expected from the simple gating scheme of Figure 7.4. Such experiments confirm directly the view of ion permeation and channel gating that we have used to explain the electrical behavior of the membranes of excitable cells. Clearly, the gated ion channels carrying electrical current across the plasma membrane are not just figments of the neurophysiologist's imagination.

The development of the patch-clamp technique has produced a flurry of new information about ion channels of all types. For example, the currents flowing through single voltage-sensitive sodium and potassium channels that underlie the action potential (see chapters 5 and 6) have also been observed using this technique.

Figure 7.15
The molecular structure of the acetylcholine-activated channel, shown from the side and from above. The five subunits interact to form the gated ion channel of the end-plate membrane.

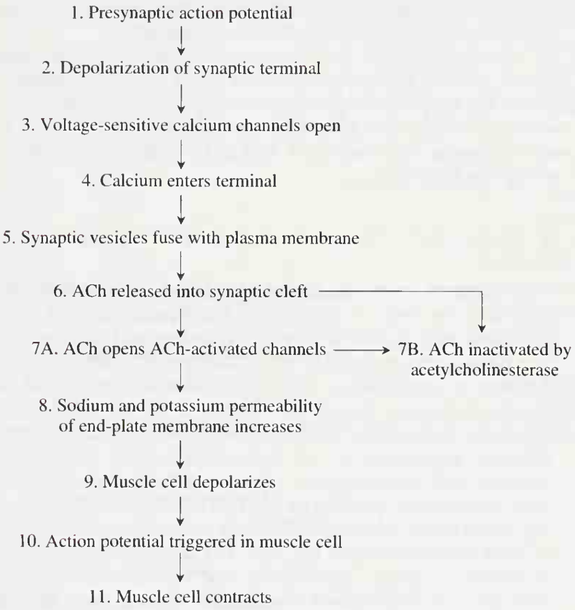


Molecular properties of the acetylcholine-activated channel

Techniques of molecular biology are being applied with great success to the study of ion-channel function, particularly when combined with measurements of single-channel behavior using the patch-clamp technique. This strategy has been especially effective in investigations of the ACh-activated channel of the muscle end-plate. Biochemical studies have shown that this channel is formed by the aggregation of five individual protein subunits: two copies of an alpha-subunit, plus single beta-, gamma-, and delta-subunits. The two ACh-binding sites have been located, one on each of the two alpha-subunits, accounting neatly for the binding of two ACh molecules that is required to open the channel (see Fig. 7.4). The subunits come together as shown in Figure 7.15 to create the ACh-activated channel, with parts of each subunit forming the aqueous pore through which cations can cross the membrane. The genes encoding each of these subunits have been identified and analyzed, and the sequence of amino acids making up the protein has been deduced by reading the relevant genetic code from the nucleic-acid pattern in the DNA. This sequence of amino acids gives valuable structural information about the ACh-activated channel.

Molecular biological techniques can also be used to assign functional roles to particular parts of the channel protein. This approach uses the fact that it is possible to make messenger RNA from the DNA sequence of the channel protein. When this mRNA is injected into a cell that does not normally produce ACh-activated channels (such as the egg cell of a frog), the cell's protein synthesis machinery will read the message and create functional channels. The properties of these channels can then be examined using patch-clamp recording. By altering the mRNA, experimenters can then make discrete changes in the channel protein and see how the modification affects the channel's behavior. For example, this technique has been employed to identify the parts of each subunit that probably make up the ion-conducting pore.

Figure 7.16
Summary of the sequence of events during synaptic transmission at the neuromuscular junction.


1. Presynaptic action potential
2. Depolarization of synaptic terminal
3. Voltage-sensitive calcium channels open
4. Calcium enters terminal
5. Synaptic vesicles fuse with plasma membrane
6. ACh released into synaptic cleft
7A. ACh opens ACh-activated channels
7B. ACh inactivated by acetylcholinesterase
8. Sodium and potassium permeability of end-plate membrane increases
9. Muscle cell depolarizes
10. Action potential triggered in muscle cell
11. Muscle cell contracts

SUMMARY

The sequence of events during synaptic transmission at the neuromuscular junction is summarized in Figure 7.16. The depolarization produced by an action potential in the synaptic terminal opens voltage-dependent calcium channels in the terminal membrane. Calcium ions enter the terminal down their concentration and electrical gradients, inducing acetylcholine-filled synaptic vesicles to fuse with the plasma membrane facing the muscle cell. The ACh is then dumped into the synaptic cleft, where some of it diffuses to the muscle membrane and combines with specific receptors on ACh-activated channels in the muscle membrane. Binding of ACh causes the channel to open and allows sodium and potassium ions to cross the membrane. The muscle membrane becomes depolarized, which triggers an all-or-nothing action potential in the muscle cell. The action of ACh is terminated by the enzyme acetylcholinesterase, which splits ACh into acetate and choline.

8

Synaptic Transmission in the Central Nervous System

Chemical synapses between neurons operate according to the same general principles as the synapses between motor neurons and muscle cells discussed in chapter 7. In the patellar reflex, for example, an action potential in the sensory neuron depolarizes the quadriceps motor neuron through a sequence of events similar to that observed at the neuromuscular junction. Some major differences do exist between neuron-to-neuron synapses and neuron-to-muscle synapses, however. This chapter will consider some of those differences, using again the patellar reflex as a model system.

EXCITATORY AND INHIBITORY SYNAPSES

At the neuromuscular junction, acetylcholine depolarizes the muscle cell, causing it to fire an action potential. Synapses of this type are called **excitatory synapses** because the neurotransmitter brings the membrane potential of the postsynaptic cell toward the threshold for firing an action potential, which tends to "excite" the postsynaptic cell. The synapse between the sensory neuron and the quadriceps motor neuron in the patellar reflex represents an example of an excitatory synapse between two neurons. Synapses between neurons are not always excitatory, however. At **inhibitory synapses**, the neurotransmitter keeps the membrane potential of the postsynaptic cell more negative than the threshold potential, which tends to prevent the postsynaptic neuron from firing an action potential. Thus, the postsynaptic cell is said to be "inhibited" by the release of the inhibitory neurotransmitter. The fact that not all synapses in the nervous system are excitatory is one major difference between synaptic transmission at the neuromuscular junction and synaptic transmission in the nervous system in general.

We will return to inhibitory synapses later in this chapter. In the following sections, our discussion will focus on the properties of excitatory synaptic transmission between neurons in the nervous system.

EXCITATORY SYNAPTIC TRANSMISSION BETWEEN NEURONS

The synapse at the neuromuscular junction is unusual in one important regard: a single action potential in the presynaptic motor neuron produces a sufficiently large depolarization in the postsynaptic muscle cell to trigger a postsynaptic action potential. In such a "one-for-one" synapse, one action potential appears in the output cell for each action potential generated in the input cell. Most synapses between neurons are not so strong, however. Instead, a single presynaptic action potential usually produces only a small depolarization of the postsynaptic cell. The synapse between a single stretch receptor sensory neuron and a quadriceps motor neuron is typical of this situation, as demonstrated in Figure 8.1.

Temporal and spatial summation of synaptic potentials

Figure 8.1A shows an experimental arrangement for recording the change in the membrane potential of a motor neuron when a single presynaptic sensory neuron is stimulated to fire an action potential. In this case, an intracellular probe is placed inside the sensory fiber, allowing an action potential to be triggered by delivery of a depolarizing current into the nerve fiber. Figure 8.1B shows sample results when a single action potential is triggered in the sensory neuron and when four action potentials are triggered in rapid sequence. A single presynaptic action potential produces only a small depolarizing change in the motor neuron's membrane potential, known as an **excitatory postsynaptic potential** (e.p.s.p.). A single e.p.s.p. is typically

Figure 8.1
Synaptic transmission at an excitatory synapse between two neurons. (A) An experimental arrangement for examining transmission between a sensory and a motor neuron in the patellar reflex loop.

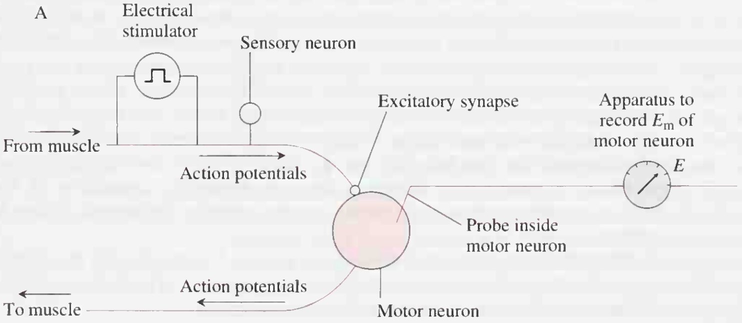
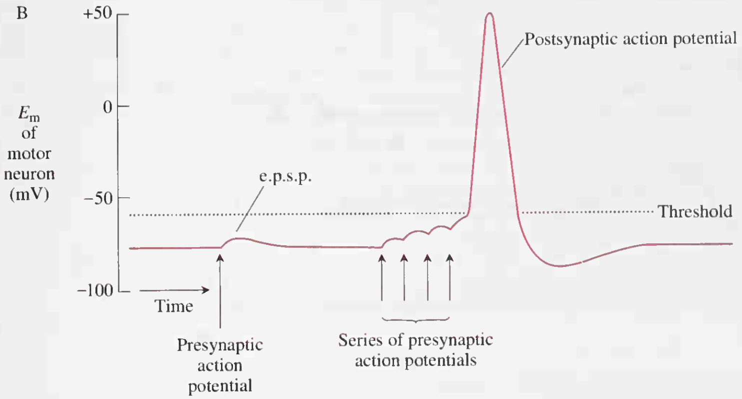


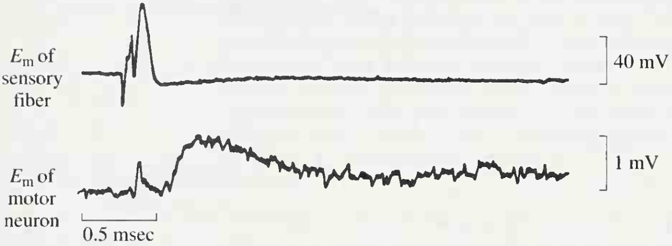
Figure 8.1 (continued)
(B) Responses of the postsynaptic motor neuron to action potentials in the presynaptic sensory neuron. At the upward arrows, action potentials are triggered in the presynaptic neuron by an electrical stimulus.



much too small to reach the threshold level for triggering a postsynaptic action potential.

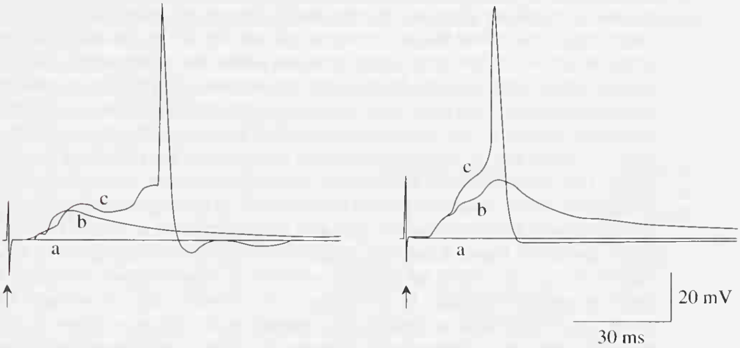
Figure 8.2 shows an actual recording of an e.p.s.p. in a motor neuron produced by an action potential in a single sensory neuron. In this experiment, an intracellular electrode was placed inside the sensory fiber to record the presynaptic membrane potential and to inject depolarizing current that elicited an action potential in the presynaptic fiber (upper recording trace). A second intracellular electrode in the motor neuron recorded the change in membrane potential of the postsynaptic cell (see Fig. 8.1A). If a second action potential arrives at the presynaptic terminal before the postsynaptic effect of the first action potential has disappeared, the second e.p.s.p. will sum with the first to produce a larger peak postsynaptic depolarization. If a series of action potentials arrives in the presynaptic terminal in rapid order, the individual e.p.s.p.'s could add up to a depolarization that reaches the threshold (see Fig. 8.1B). This summation of sequential postsynaptic effects of an individual presynaptic input, called **temporal summation**, is an important mechanism by which even a weak excitatory synaptic input can cause a neuron to fire an action potential. Figure 8.3 shows actual recordings illustrating temporal summation of e.p.s.p.'s. Each set of traces consists of superimposed responses to three presynaptic stimuli. In each case, one stimulus fails to activate the presynaptic input and so produces no postsynaptic response (trace a), one stimulus produces a postsynaptic response that fails to reach threshold (trace b), and one stimulus produces a postsynaptic response that reaches threshold

Figure 8.2
Simultaneous intracellular recordings from a single stretch-sensitive sensory nerve fiber and a motor neuron receiving synaptic input from the sensory fiber. An action potential was triggered in the sensory fiber by passing a depolarizing electrical current through the intracellular electrode. After a brief delay, a small excitatory postsynaptic potential was evoked in the postsynaptic motor neuron.



(Unpublished data provided by W. Collins, M. Honig, and L. Mendell of the State University of New York at Stony Brook.)

Figure 8.3
Intracellular recordings of excitatory postsynaptic potentials in a neuron, showing summation of successive e.p.s.p.'s. Each set of traces shows three superimposed responses. The arrow indicates the electrical stimulus used to trigger action potentials in the presynaptic neurons that make excitatory synapses onto the recorded cell. Trace *a* in each set shows a stimulus that failed to trigger the presynaptic input. Trace *b* shows e.p.s.p.'s that failed to reach threshold. Trace c shows summated e.p.s.p.'s that reached threshold and produced a postsynaptic action potential. In this figure, the postsynaptic cell is a motor neuron of the sympathetic nervous system.



(Unpublished data provided by H.-S. Wang and D. McKinnon of the State University of New York at Stony Brook.)

and triggers a postsynaptic action potential (trace c). Only if the successive e.p.s.p.'s summate sufficiently to reach threshold is an action potential triggered in the postsynaptic cell.

Another way that e.p.s.p.'s can sum to reach the threshold is via the simultaneous firing of action potentials by several presynaptic neurons. In reality, a single neuron in the nervous system (such as the motor neuron in Figure 8.1) receives synaptic inputs from hundreds or even thousands of presynaptic neurons. In the patellar reflex, for example, a single quadriceps motor neuron will receive excitatory synaptic connections from many stretch receptor sensory neurons (Fig. 8.4A). A single action potential in any of these presynaptic cells produces only a small postsynaptic depolarization (Fig. 8.4B). If several presynaptic cells fire simultaneously, however, their postsynaptic effects add up and can reach the threshold. This type of **spatial summation** occurs when a single postsynaptic cell receives spatially distinct inputs.

In the patellar reflex, both temporal and spatial summation are important in eliciting the reflexive response. To produce reflexive contraction of the quadriceps muscle, a tap to the patellar tendon must stretch the muscle sufficiently to fire a number of action potentials in each of a number of individual sensory neurons.

Some possible excitatory neurotransmitters

The chemical neurotransmitter at the neuromuscular junction has been conclusively demonstrated to be acetylcholine, as discussed in chapter 7. Acetylcholine is also used as a neurotransmitter at some neuron-to-neuron synapses. In addition, many other substances are excitatory neurotransmitters in the nervous system. As shown in Figure 8.5, many excitatory neurotransmitters are relatively small molecules, often derived by simple chemical modifications to amino acids. Amino acids are more commonly thought of as the basic building blocks for the construction of proteins; in the nervous system, however, amino acids are often used for cell-to-cell signaling in neurotransmission. For example, glutamate and aspartate are unmodified amino acids, while norepinephrine and dopamine are derived from the amino acid tyrosine and serotonin is derived from tryptamine. Some evidence suggests that glutamate may serve as the excitatory transmitter at the synapse between the sensory and motor neurons in the patellar reflex.

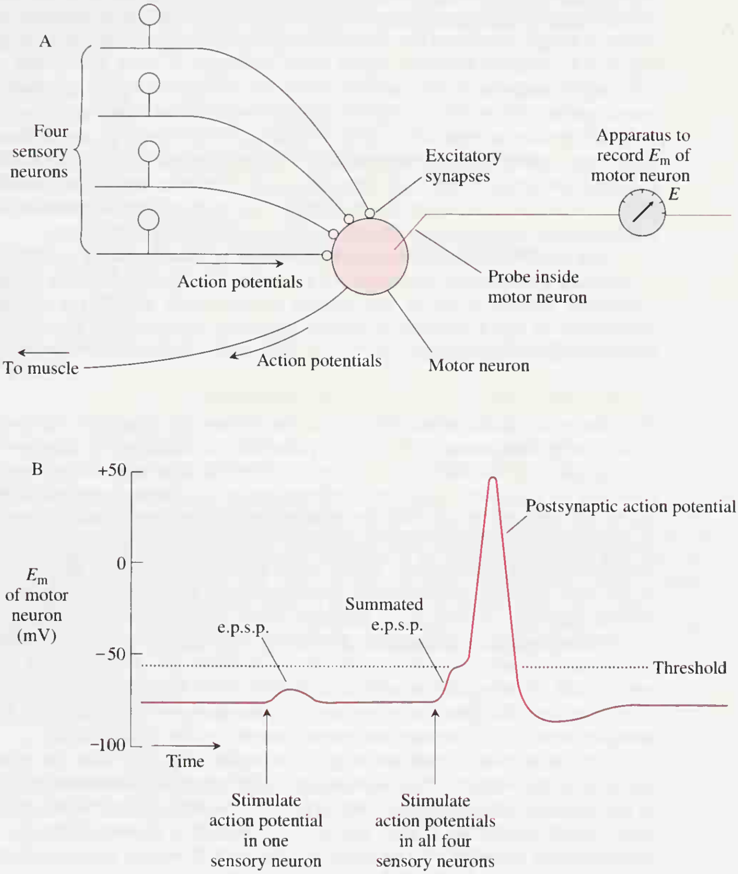
Other neurotransmitters are more structurally complex than the small amino-acid derivatives. These substances—called peptide neurotransmitters, or more simply **neuropeptides**—are formed from a series of individual amino acids linked by peptide bonds, like a small piece of a protein molecule. A representative member of this class is substance P, whose amino-acid sequence is shown in Figure 8.5.

The list of excitatory neurotransmitters given in Figure 8.5 is by no means exhaustive. As our knowledge of the brain grows, it is likely that many new candidates will be added to this list.

Conductance-decrease e.p.s.p.'s

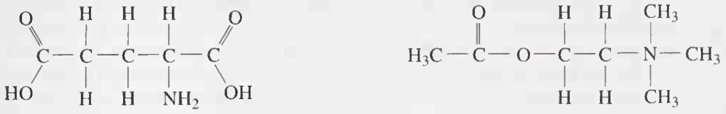
In most cases, the mechanism by which an excitatory neurotransmitter produces an e.p.s.p. in the postsynaptic cell is the same as that by which

Figure 8.4
Spatial summation of excitatory inputs to a motor neuron.


A
Four sensory neurons
Excitatory synapses
Apparatus to record E_m of motor neuron
E
Action potentials
Probe inside motor neuron
To muscle
Action potentials
Motor neuron
B
+50
0
−50
−100
E_m of motor neuron (mV)
Time
e.p.s.p.
Summated e.p.s.p.
Postsynaptic action potential
Threshold
Stimulate action potential in one sensory neuron
Stimulate action potentials in all four sensory neurons

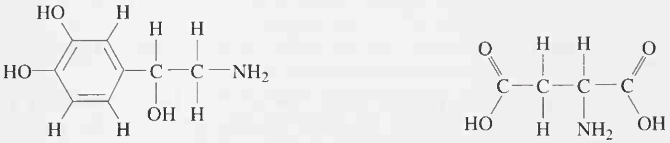
acetylcholine depolarizes the muscle at the neuromuscular junction. That is, the transmitter opens channels in the postsynaptic membrane through which sodium and potassium ions (or just sodium ions) can cross. The altered balance of sodium and potassium permeability causes the membrane potential to shift in a positive direction. In terms of the ionic current flowing across

Figure 8.5
Structures of some substances likely to be excitatory neurotransmitters in the nervous system.



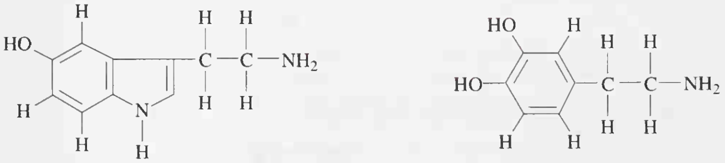
Glutamic acid
(Glutamate)

Acetylcholine



Norepinephrine

Aspartic acid
(Aspartate)



Serotonin
(5-hydroxytryptamine)

Dopamine

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Substance P
(a string of 11 amino acids attached by peptide bonds)

the postsynaptic membrane, the excitatory neurotransmitter acts to increase the relative sodium conductance of the postsynaptic membrane, so that the balance between inward sodium current and outward potassium current is struck slightly nearer E_{Na}.

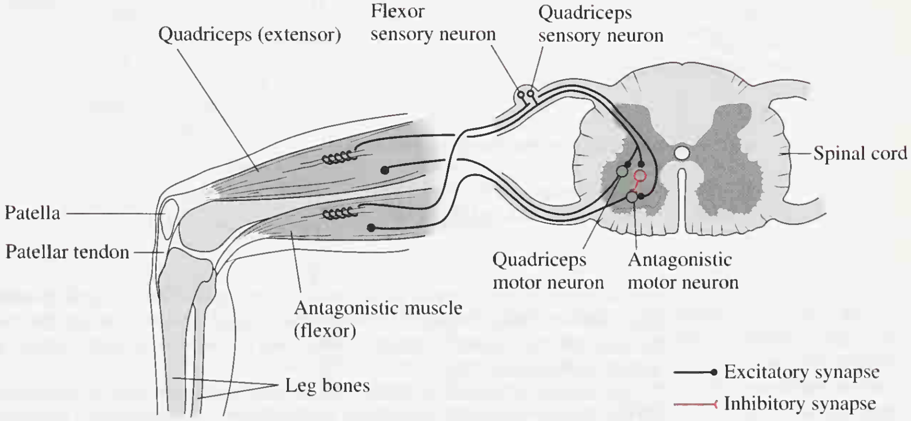
As we saw in chapter 4, however, the membrane potential is controlled by the ratio of sodium to potassium permeability. Consequently, a depolarization might result from either an increase in sodium permeability or a decrease in potassium permeability. Indeed, at some synapses, the effect of the transmitter is mediated via a reduction in the potassium conductance of the postsynaptic neuron. For instance, acetylcholine produces a long-lasting depolarization of sympathetic ganglion neurons in the frog. This depolarization appears to be mediated by a decrease in the potassium permeability of the neuron; acetylcholine causes a type of potassium channel in the neuron membrane to close, so that the outward potassium current across the membrane declines and the resting inward sodium current exerts a greater influence on the membrane potential.

INHIBITORY SYNAPTIC TRANSMISSION

The synapse between sensory neurons and antagonist motor neurons in the patellar reflex

The diagram for the patellar reflex that we have been considering since chapter 5 is not really quite complete. Muscles other than the quadriceps must be considered as well (Fig. 8.6). For example, muscles at the back of the thigh that are attached to the lower leg bones are responsible for flexion of the knee joint, just as the quadriceps is responsible for extension of the knee joint. These flexor muscles, which are antagonistic to the action of the quadriceps, have their own stretch-sensitive sensory neurons and motor

Figure 8.6
A revised diagram of the circuitry involved in stretch reflexes of thigh muscles.



neurons that are connected in a reflex chain, just like those of the quadriceps. As a result, a stretch of the flexor muscle stimulates action potentials in the sensory neurons, which create excitatory synapses on the motor neurons that cause the same muscle to contract.

When the patellar tendon is tapped, the quadriceps muscle reflexively contracts, causing the knee joint to extend (the "jerk" of the knee-jerk reflex). The extension of the joint stretches the flexor muscles at the back of the thigh, which should then contract because of the action of their own stretch-reflex mechanism. The resulting flexion of the joint should stretch the quadriceps again and elicit a reflexive extension, which should elicit another reflexive flexion, and so on. One might expect that a single tap to the patellar tendon would send the knee joint into a series of oscillations that would continue until muscle exhaustion set in.

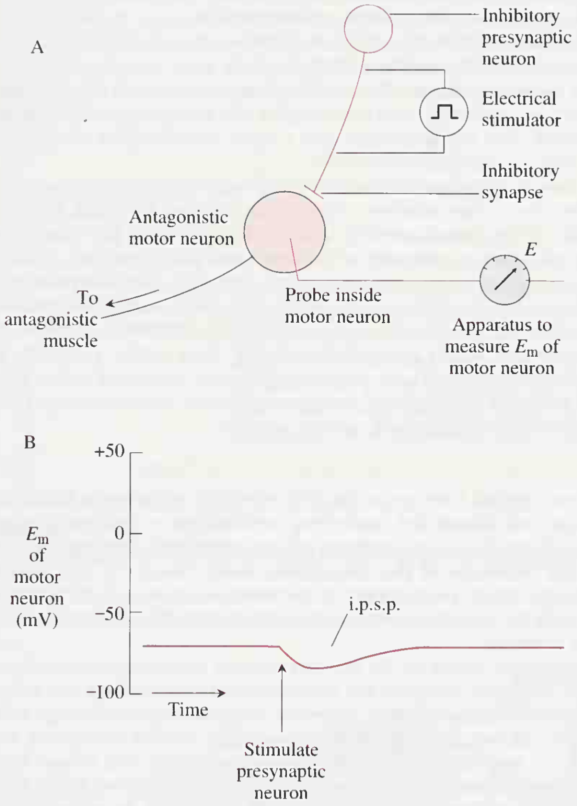
Why, then, does tapping the patellar tendon elicit only a single knee jerk? The answer lies in the neuronal circuitry diagrammed in Figure 8.6. The nerve fibers of the stretch-sensitive sensory neurons from the quadriceps muscle actually branch profusely when they enter the spinal cord, making synaptic connections with many kinds of neurons other than the quadriceps motor neuron. For example, the sensory neurons make excitatory synapses on a type of spinal interneuron that in turn makes inhibitory synapses on the motor neurons of the antagonistic muscles. Thus, action potentials in quadriceps sensory neurons not only tend to excite quadriceps motor neurons, but also tend indirectly to prevent antagonistic motor neurons from being excited by the antagonistic sensory neurons.

Characteristics of inhibitory synaptic transmission

We will now consider some properties of postsynaptic responses at an inhibitory synapse and discuss the underlying mechanisms in the postsynaptic membrane. Figure 8.7 shows schematically an experimental arrangement to examine the inhibition of the antagonistic motor neuron in the patellar reflex. An intracellular probe monitors the membrane potential of the motor neuron, while the inhibitory presynaptic neuron is stimulated electrically to fire action potentials.

Presynaptically, release of the neurotransmitter follows the same scheme as at other chemical synapses: the depolarization produced by the action potential permits calcium ions to enter the synaptic terminal through voltage-sensitive calcium channels, inducing synaptic vesicles containing the transmitter to fuse with the membrane of the terminal and release their contents. Postsynaptically, the transmitter has a very different effect than acetylcholine at the neuromuscular junction (see Fig. 8.7B). An action potential in the presynaptic cell is followed by a transient increase in the postsynaptic membrane potential. When the membrane potential becomes more negative, the cell is said to be **hyperpolarized.** Because a hyperpolarization moves the membrane potential away from the threshold for firing an action potential, an excitatory input is less likely to trigger an action potential and the postsynaptic cell is inhibited. The change in the postsynaptic cell's membrane potential that is induced by the release of an inhibitory neurotransmitter is called an **inhibitory postsynaptic potential** (i.p.s.p.).

Figure 8.7
Inhibitory synaptic transmission between two neurons in the circuit shown in Figure 8.6. An action potential in the presynaptic neuron releases a neurotransmitter that hyperpolarizes the postsynaptic neuron.


A
Inhibitory presynaptic neuron
Electrical stimulator
Inhibitory synapse
Antagonistic motor neuron
E
To antagonistic muscle
Probe inside motor neuron
Apparatus to measure E_m of motor neuron
B
+50
0
-50
-100
E_m of motor neuron (mV)
i.p.s.p.
Time
Stimulate presynaptic neuron

Mechanism of inhibition in the postsynaptic membrane

A recurring theme in our discussion of cell function has been that changes in ionic permeability of the plasma membrane lead to changes in membrane potential. The i.p.s.p. is no different in this regard. When the permeability of the membrane to a particular ion increases, the membrane potential tends to move toward the equilibrium potential for that ion. In chapter 5, we saw how this sort of mechanism can explain the sequence of potential changes during an action potential.

To see how a hyperpolarizing response might result from a change in ionic permeability, consider the situation diagrammed in Figure 8.8. If potassium permeability of a cell membrane were suddenly increased, the membrane potential would be expected to move toward E_K, which is approximately -85 mV for a typical mammalian cell (see chapters 3 and 4). In this situation, p_{Na}/p_K would be smaller than usual, and the balance between potassium and sodium would be struck closer to E_K. A similar situation arises during the undershoot at the end of an action potential, when p_{Na}/p_K becomes transiently smaller than normal. Thus, an inhibitory transmitter could hyperpolarize the postsynaptic cell by opening potassium channels in the postsynaptic membrane (see Fig. 8.8B). Like the action of acetylcholine at the neuromuscular junction, the inhibitory transmitter would affect permeability by combining with specific binding sites associated with the ion channel. When the binding sites become occupied, the gate controlling movement through the channel would open, allowing potassium ions to move out of the cell and drive E_m closer to the potassium equilibrium potential.

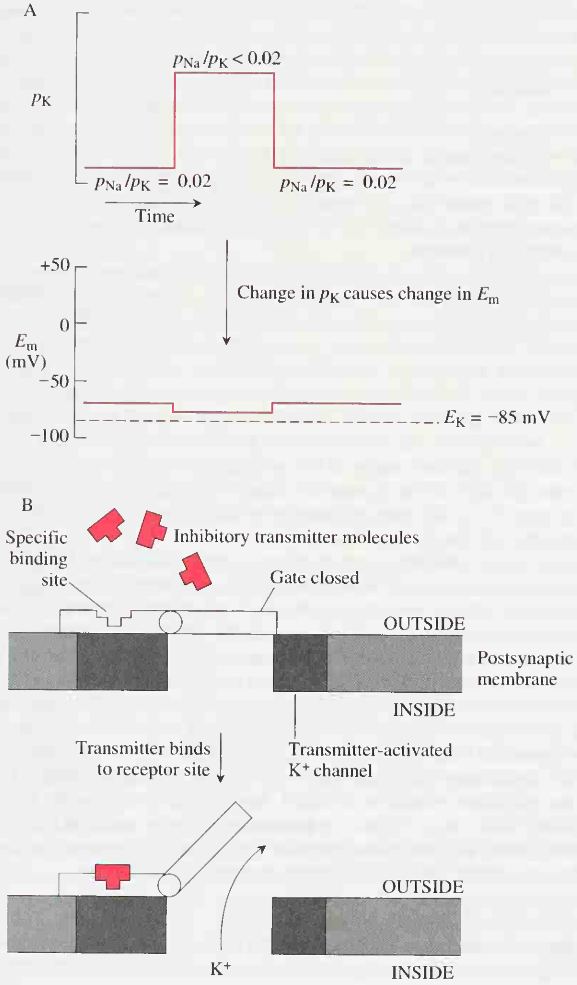
At most inhibitory synapses, however, the transmitter-activated postsynaptic channels are not potassium channels. Instead, most inhibitory neurotransmitters open postsynaptic channels that permit chloride ions to cross the membrane. Recall from chapters 3 and 4 that chloride pumps in the plasma membrane maintain a chloride equilibrium potential, E_{Cl}, that is more negative than the resting membrane potential in many nerve cells. Thus, the electrical gradient driving chloride out of the cell at the normal resting E_m is weaker than the concentration gradient driving chloride into the cell. If chloride channels open in the postsynaptic membrane, chloride ions will enter the cell, bringing negative charge into the cell and hyperpolarizing the neuron. In this way, an increase in the chloride permeability of the postsynaptic cell can produce an i.p.s.p.

In general terms, inhibition results when a neurotransmitter induces a permeability increase to an ion with an equilibrium potential more negative than the threshold level of membrane potential. Ions always move across the membrane in a direction that moves E_m toward the equilibrium potential for that ion. If that equilibrium potential is more negative than the threshold level, the ion will *oppose* any attempt to reach the threshold as soon as the depolarization exceeds the ion's equilibrium potential. Seen in this light, an inhibitory permeability increase could occur without any visible change in membrane potential from its resting level. This would occur, for example, if the chloride equilibrium potential were equal to the resting potential. The effect of the inhibition would be revealed, however, if an excitatory input were activated while the inhibitory permeability increase remained active. The excitatory effect on membrane potential would then be lessened because of the enhanced ability of chloride ions to oppose depolarization.

Some possible inhibitory neurotransmitters

The identity of the chemical neurotransmitter at many inhibitory synapses within the nervous system remains unknown, although some likely

Figure 8.8
The mechanism by which an inhibitory postsynaptic potential might be produced in a postsynaptic neuron. (A) An increase in potassium permeability would be expected to cause a more negative membrane potential. (B) A neurotransmitter-activated potassium channel in the plasma membrane of a postsynaptic neuron at an inhibitory synapse.



candidates have been identified (Fig. 8.9). Of those substances shown in the figure, GABA and glycine are almost certainly transmitters at certain inhibitory synapses in the nervous system.

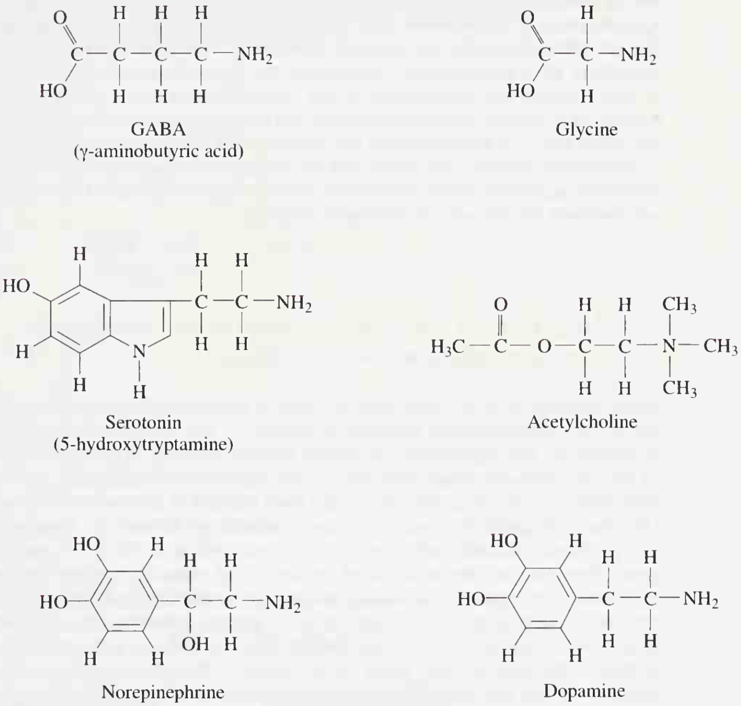
Some of the inhibitory neurotransmitter candidates also appeared in the list of candidate excitatory neurotransmitters (see Fig. 8.5). This overlap appears because a transmitter may have an excitatory effect on one neuron but an inhibitory effect on another. Whether a substance is excitatory or inhibitory for a given neuron depends on the type of ion channel it opens in the postsynaptic membrane. If the transmitter-activated channel is a sodium or a sodium–potassium channel (as at the neuromuscular junction), the effect will be a depolarization and excitation; if the channel is a chloride or potassium channel, the effect will be hyperpolarization and inhibition. The same neurotransmitter could even produce opposite effects at two different synapses on the same postsynaptic neuron.

The Family of Neurotransmitter-Gated Ion Channels

In our discussion of the molecular structure of the acetylcholine-gated channel at the neuromuscular junction in chapter 7, we saw that the channel is formed by the aggregation of several protein subunits. The other kinds of ion channels described here—those that underlie excitatory and inhibitory postsynaptic potentials—have also been studied at the molecular level. Like the ACh-gated channel, these ion channels are formed by aggregates of individual subunits, with each type of subunit encoded by a specific gene. Nevertheless, the amino-acid sequences of subunits making up the neurotransmitter-gated channels are all roughly similar. For example, GABA-activated channels are structurally similar to glycine-activated channels and to ACh-activated channels; glutamate-activated channels are related to ACh-activated channels as well, albeit more distantly. The genes coding for the subunits of the ion channels opened by neurotransmitters form a related family of genes, called the **ligand-gated ion channel family.** As the name suggests, members of the family form ion channels that are opened by the binding of a chemical signal (the ligand) to a specific binding site on the channel.

Of course, there are also important functional differences among the members of this gene family. First, each channel type must exhibit specificity for activation by a particular neurotransmitter: a glutamate-activated channel is not activated by GABA, even though glutamate and GABA are structurally quite similar (see Figs. 8.5 and 8.9). (In fact, GABA is formed enzymatically by modification of glutamate.) Thus, the part of the protein that constitutes the binding site for each type of neurotransmitter must possess certain unique features. Second, important differences are found among members of the ligand-gated ion channel family in terms of the properties of the pore through which ions can cross the membrane when

Figure 8.9
Structures of some substances likely to act as inhibitory neurotransmitters in the nervous system.



GABA
(γ-aminobutyric acid)

Glycine

Serotonin
(5-hydroxytryptamine)

Acetylcholine

Norepinephrine

Dopamine

Tyr-Gly-Gly-Phe-Leu
Leucine enkephalin
(a series of five amino acids connected by peptide bonds)

the channel is open. Some ligand-gated channels form cation pores (for example, glutamate channels or ACh channels), while others form anion pores (for example, glycine or GABA channels). This difference in ionic selectivity reflects underlying differences in how the pore region is constructed.

INDIRECT ACTIONS OF NEUROTRANSMITTERS

In our discussions of neurotransmitter action, both at the neuromuscular junction in chapter 7 and in the central nervous system in this chapter, we have considered only direct effects of the transmitter on the postsynaptic cell's ionic permeability. In such direct actions, the receptor (binding site) to which the neurotransmitter molecules bind constitutes part of the ion-channel protein (see Figs. 7.4 and 8.8). In a wide variety of postsynaptic effects produced by neurotransmitters, however, the receptor comprises a separate protein from the ion channel and the linkage between the two is indirect. Such mechanisms allow a single neurotransmitter to have numerous and diverse effects on a postsynaptic neuron—for example, closing ion channels of one class while opening others, affecting the metabolism of the postsynaptic cell as well as its membrane permeability, or altering gene expression.

The basic scheme for such indirect actions is shown in Figure 8.10. The first two steps (presynaptic release of neurotransmitter and binding of neurotransmitter to specific postsynaptic receptor) are the same as those seen with the direct actions of neurotransmitter that we considered earlier. What happens next, however, differs dramatically from the ligand-gated channel family. The combination of the transmitter with its receptor causes the postsynaptic cell to release internally a substance, called a **second messenger** (the neurotransmitter is the first messenger), that alters the state of the postsynaptic cell. The list of second-messenger molecules continues to grow as we learn more about the basic cell biology of indirect neurotransmitter actions. Known second messengers include the following:

- Cyclic AMP (cyclic adenosine monophosphate), which is produced from ATP by the enzyme adenylate cyclase.

- Cyclic GMP (cyclic guanosine monophosphate), which is produced from GTP (the guanine nucleotide equivalent of ATP) by the enzyme guanylate cyclase.

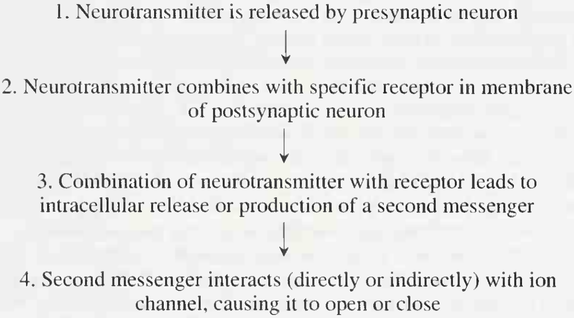
- The dual second messengers diacylglycerol and inositol trisphosphate, both of which are produced from a particular kind of membrane lipid molecule by the enzyme phospholipase C.

- Arachidonic acid, which is produced from membrane lipid by the enzyme phospholipase A.

The effect that the second messenger has on the cell varies according to the situation. If it causes sodium channels to open or potassium channels to close, for instance, the postsynaptic neuron would tend to be excited. Conversely, if the second messenger initiates opening of potassium or chloride channels, or closing of sodium channels, then the net result would be inhibition of the postsynaptic cell.

How are the second messenger and the target ion channel linked? In some cases, the second messenger directly combines with the ion channel, causing it to open. This occurs in the photoreceptor cells of the retina, for

Figure 8.10
An overview of the indirect linkage of a neurotransmitter to activity of an ion channel via an intracellular second messenger in the postsynaptic cell.



1. Neurotransmitter is released by presynaptic neuron
2. Neurotransmitter combines with specific receptor in membrane of postsynaptic neuron
3. Combination of neurotransmitter with receptor leads to intracellular release or production of a second messenger
4. Second messenger interacts (directly or indirectly) with ion channel, causing it to open or close

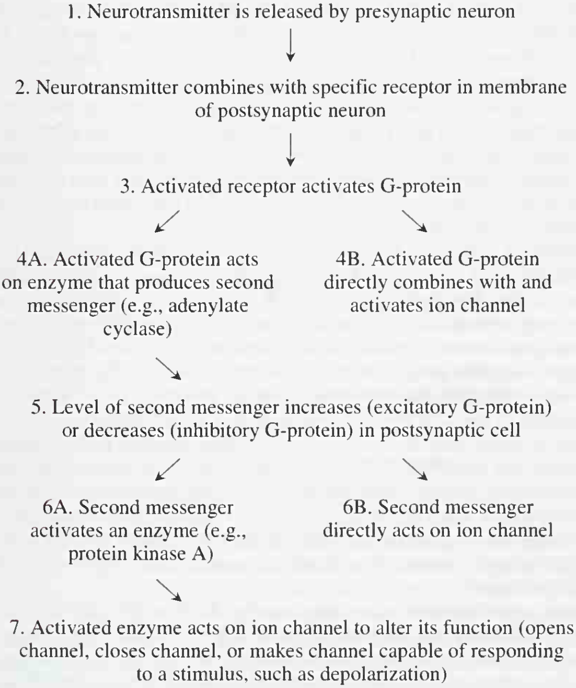
example, where cyclic GMP opens cation channels in the plasma membrane. In other instances, the second messenger acts indirectly, by activating an enzyme that then affects the ion channel. For example, cyclic AMP activates an enzyme called cyclic-AMP–dependent protein kinase (or protein kinase A). The protein kinase phosphorylates proteins, including ion channels, which is a common biochemical mechanism by which protein function is altered. (In phosphorylation, inorganic phosphate—derived from splitting ATP into ADP and phosphate—becomes attached to a specific site on the target protein by the protein-kinase enzyme.) In neurons, for example, phosphorylation of voltage-activated calcium channels is thought to be necessary for normal operation of the channel (that is, phosphorylated channels open upon depolarization, while non-phosphorylated channels remain inactive). In this way, a neurotransmitter might indirectly affect calcium-channel function in a postsynaptic cell by altering the level of cyclic AMP.

Binding of a neurotransmitter to its postsynaptic receptor can, therefore, activate an enzyme that produces a second messenger; this messenger can, in turn, directly or indirectly affect ion permeability of the postsynaptic cell. What is the nature of the linkage between the activated receptor and the enzyme that generates the second messenger? Once again, the linkage is indirect and involves yet another protein. This GTP-binding protein, or **G-protein**, is so named because binding of GTP is required for its activation. In its inactivated state, the G-protein has GDP bound to it; the activated neurotransmitter receptor catalyzes the replacement of GDP by GTP and thus the activation of the G-protein. The activated G-protein then interacts with and stimulates the enzyme producing the second messenger (adenylate cyclase in the case of cyclic AMP, for example).

Various kinds of G-protein have been identified, each of which exerts specific effects on specific target enzymes. For example, some G-proteins stimulate the activity of the target enzyme, while others inhibit it. As a result, neurotransmitter activation of one receptor might increase the level of a second messenger, while activation of a different receptor might decrease the level of the second messenger, depending on the type of G-protein to which the receptor is coupled. In addition to acting via second messengers, activated G-protein may sometimes serve as a messenger that directly activates ion channels.

The indirect actions of neurotransmitters are summarized in the sequence of events shown in Figure 8.11. We can envision this sequence as an enzymatic cascade, where an activated neurotransmitter receptor acts as an enzyme to activate G-protein, which in turn activates an enzyme that produces

Figure 8.11
The sequence of events in the indirect action of a neurotransmitter on membrane permeability of a postsynaptic cell. Ion-channel activity may be altered by G-proteins, second messengers, or second-messenger–dependent enzymes.



1. Neurotransmitter is released by presynaptic neuron

2. Neurotransmitter combines with specific receptor in membrane of postsynaptic neuron

3. Activated receptor activates G-protein

4A. Activated G-protein acts on enzyme that produces second messenger (e.g., adenylate cyclase)

4B. Activated G-protein directly combines with and activates ion channel

5. Level of second messenger increases (excitatory G-protein) or decreases (inhibitory G-protein) in postsynaptic cell

6A. Second messenger activates an enzyme (e.g., protein kinase A)

6B. Second messenger directly acts on ion channel

7. Activated enzyme acts on ion channel to alter its function (opens channel, closes channel, or makes channel capable of responding to a stimulus, such as depolarization)

a second messenger, which in turn activates another enzyme that influences ion-channel operation. In this sequence, an ion channel might be affected at three different points:

- Activated G-protein might bind to and activate an ion channel.
- The second messenger might directly bind to the channel.
- An enzyme, such as a protein kinase, that depends on the presence of the second messenger might act on the ion channel.

In all cases, the neurotransmitter's net excitatory or inhibitory effect will depend on the type of ion channel affected in the postsynaptic membrane and on whether the ion channel tends to be activated or inactivated by the indirect action of the neurotransmitter.

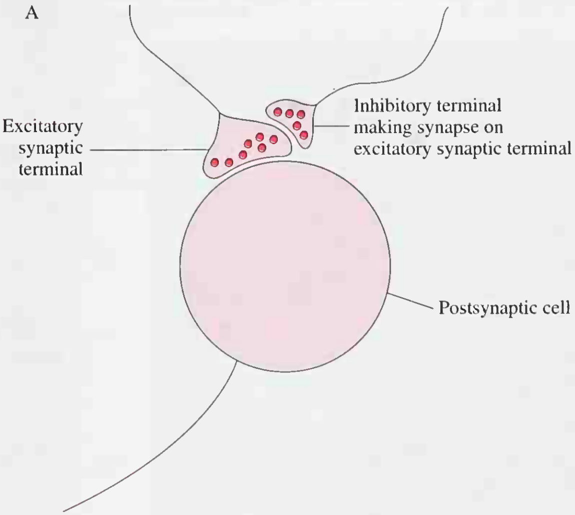
PRESYNAPTIC INHIBITION AND FACILITATION

A different form of inhibitory interaction is sometimes observed among neurons in the nervous system. In the case we discussed earlier (see Fig. 8.8), inhibition is accomplished by altering directly the membrane permeability of the postsynaptic cell. In the other type of inhibition, it is exerted indirectly through the membrane of an excitatory presynaptic terminal. In this latter type of inhibition, called **presynaptic inhibition** (Fig. 8.12), the inhibitory terminal reduces the influx of calcium into the excitatory synaptic terminal during an action potential. As a result, fewer synaptic vesicles fuse with the membrane of the excitatory terminal and the release of excitatory transmitter onto the postsynaptic neuron is reduced.

The inhibitory input can lead to a reduction of calcium influx into the excitatory terminal in a number of ways. One possible mechanism involves a reduction in the depolarization produced by an action potential in the excitatory presynaptic terminal. A smaller depolarization would open fewer voltage-sensitive calcium channels, allowing less calcium to enter the excitatory terminal. Another possibility would be a decrease in the number of voltage-sensitive calcium channels that are in the phosphorylated state and are thus capable of opening upon depolarization. Calcium influx might also be inhibited by decreasing the duration of the action potential in the presynaptic terminal—for instance, by increasing the number of voltage-sensitive potassium channels, which would permit more rapid repolarization during the action potential. The electron micrograph in Figure 8.12B shows a synapse on a nerve fiber at a location where that fiber makes a synapse onto another postsynaptic neuron. This kind of arrangement might underlie presynaptic inhibition.

Of course, a synapse onto a synapse (see Fig. 8.12) might also facilitate the release of neurotransmitter from the excitatory terminal. This arrangement is known to occur, for example, in the nervous system of a sea slug, *Aplysia*. In this organism, the neurotransmitter serotonin increases the effec-

Figure 8.12
(A) A schematic arrangement for presynaptic inhibition in the nervous system. The inhibitory terminal makes synaptic contact with another synaptic terminal, rather than directly with the postsynaptic cell.


A
Excitatory synaptic terminal
Inhibitory terminal making synapse on excitatory synaptic terminal
Postsynaptic cell

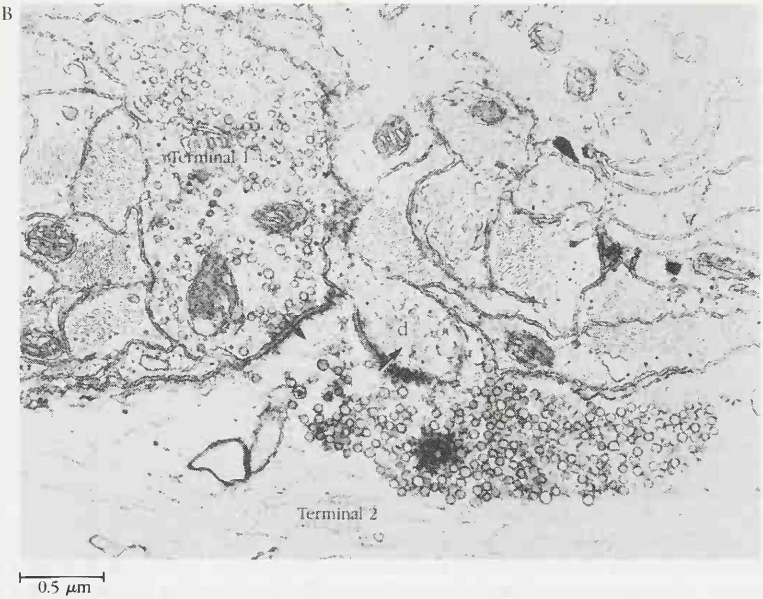
tiveness of an excitatory synaptic connection from a presynaptic sensory neuron onto a postsynaptic motor neuron by inhibiting (indirectly via a second messenger) voltage-sensitive potassium channels in the presynaptic neuron. Inhibition of these channels slows the repolarizing phase of the presynaptic action potential, prolonging the depolarization and producing greater presynaptic calcium influx and enhanced transmitter release.

NEURONAL INTEGRATION

In the nervous system, neurons receive both excitatory and inhibitory synaptic inputs. The decision of a postsynaptic neuron to fire an action potential is determined by only one factor: whether the threshold level of membrane potential has been reached. This condition can be assessed at any instant by summing all existing excitatory and inhibitory synaptic potentials. To demonstrate this relationship, we will once again consider the antagonistic motor neuron in the patellar reflex (Fig. 8.13).

Figure 8.12 (continued)
(B) An electron micrograph showing a synapse (terminal 1) in the vertebrate central nervous system onto an axon (terminal 2) that in turn makes a synapse onto a third neuronal process (labeled *d,* for dendrite). The arrows show the direction of synaptic transmission from terminal 1 to terminal 2 and from terminal 2 to the dendrite. Note the accumulations of synaptic vesicles in terminals 1 and 2.

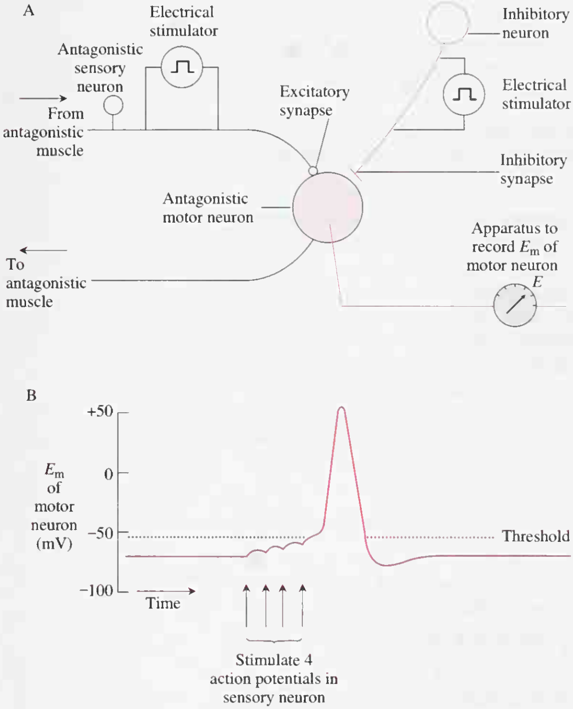
B



(B) Reproduced with permission from Wickelgren WO. Physiological and anatomical characteristics of reticulospinal neurons in lamprey. J Physiol 1977;270:89–114.

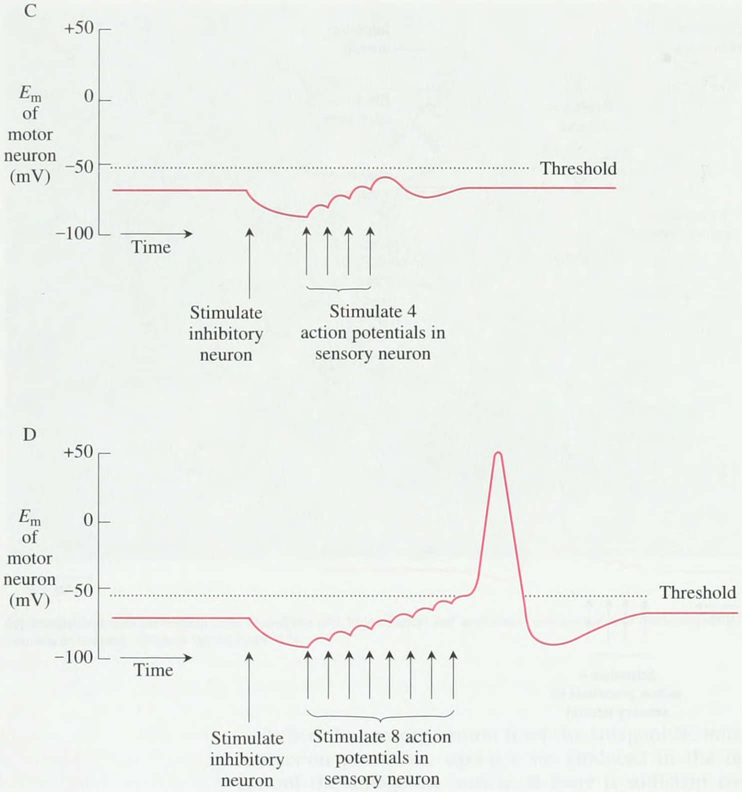
When the sensory neuron from the antagonistic muscle is stimulated to fire action potentials, e.p.s.p.'s are produced in the motor neurons that control the antagonist muscle. If there is sufficient temporal summation among the e.p.s.p.'s, an action potential will be triggered. If the inhibitory neuron is stimulated at the same time, however, the same series of excitatory inputs might prove unable to reach the threshold. This inhibitory effect could be overcome by strengthening the excitatory input, by increasing either the number of presynaptic action potentials in the sensory neuron or the number of sensory neurons activated. It is the balance between the excitatory and inhibitory inputs that dictates whether a postsynaptic action potential is generated.

Figure 8.13
The integration of excitatory and inhibitory synaptic inputs by a neuron in the nervous system. (A) An experimental arrangement for the measurements shown in B, C, and D. (B) Stimulation of the excitatory presynaptic neuron produces a postsynaptic action potential if temporal summation is sufficient to reach the threshold.



The process of summing up, or integrating, synaptic inputs onto a neuron is called **neuronal integration.** The information-processing capacity of a single neuron is considerable, as a typical neuron receives hundreds or thousands of synapses from hundreds or thousands of other neurons and makes synaptic connections itself with an equal number of postsynaptic neurons. This capacity is increased even further by the widely varying weights of synaptic inputs to a cell. Some synapses produce large changes in postsynaptic membrane potential, while others cause only tiny changes.

Figure 8.13 (continued)
(C) Stimulation of the inhibitory presynaptic neuron prevents the excitatory inputs in B from reaching the threshold. (D) The inhibitory effect can be overcome by increasing the amount of excitatory stimulation.



Furthermore, the weight given a particular input might vary with time, as in the case of presynaptic inhibition. A network of some 10^{10} of these sophisticated units, like the human brain, has staggering information-processing ability.

SUMMARY

Chemical synapses between neurons in the nervous system are similar to the synapse at the neuromuscular junction in the following ways:

- The neurotransmitter is stored in the synaptic terminal in membrane-bound synaptic vesicles.
- Influx of external calcium ions into the terminal is necessary to allow release of the neurotransmitter.
- Fusion of the synaptic vesicle with the plasma membrane of the terminal serves as the mechanism of transmitter release.
- Neurotransmitter molecules combine with specific postsynaptic receptors and open ion channels in the postsynaptic membrane.

Nervous system synapses differ from the neuromuscular junction in the following ways:

- At most synapses, a single presynaptic action potential produces only a small change in the postsynaptic membrane potential. In contrast, a single presynaptic action potential at the neuromuscular junction produces a large depolarization of the muscle cell and triggers a postsynaptic action potential.
- Synapses between neurons can be either excitatory or inhibitory.
- Acetylcholine is probably the neurotransmitter at a few synapses between neurons, but a host of other substances may potentially serve as neurotransmitters in the nervous system.
- A skeletal muscle cell receives synaptic input from only one neuron—a single motor neuron. A neuron in the nervous system may receive synaptic connections from thousands of different neurons. The output of a neuron depends on the integration of all the inhibitory and excitatory inputs active at a given instant.
- At the neuromuscular junction, ACh combines with postsynaptic binding sites that are part of the channel protein and directly opens the channel. In the central nervous system, a neurotransmitter may have either a direct effect on an ion channel or an indirect effect via an internal second messenger in the postsynaptic cell.

PART III

Motor Control Systems

In Part 2 of this book, we studied in some detail the cellular signals involved in the patellar reflex. Through those discussions, we arrived at an understanding of the membrane mechanisms that generate the action potential and that allow neurons to communicate at synapses. These fundamental neuronal signals form the basis of the nervous system's ability to transmit and analyze information.

In Part 3, we will examine that information-processing ability in somewhat more global terms. Continuing with our analysis of the patellar reflex, we will move beyond the cellular view to consider how the motor control systems of the spinal cord (including the neurons of the patellar reflex) are organized to allow flexible, yet rapid, control of fundamental aspects of the musculoskeletal apparatus, such as muscle length, joint position, and response to external loads. To understand these control systems, we must first discuss some of the mechanical properties of muscles; chapter 9 is devoted to this task, starting with a description of the contractile mechanism of individual muscle fibers. In chapter 10, we will describe spinal cord reflex circuits other than the patellar reflex. In chapters 11 and 12, we will move up the control ladder to brainstem and other brain motor systems. Chapter 13 will describe a different type of motor control system—the autonomic nervous system, which controls other motor targets such as the heart.

9

Neural Control of Muscle Contraction

In previous chapters, we have used the patellar reflex as an example system to explore the cellular signals underlying nervous system function. The final stage of the patellar reflex is the contraction of the quadriceps muscle, which occurs through the activity of the motor neurons making excitatory synaptic connections with that muscle. The arrival of an action potential in the synaptic terminal of the motor neuron stimulates the release of the chemical neurotransmitter, acetylcholine. The acetylcholine then depolarizes the end-plate region of the postsynaptic muscle cell, initiating an action potential in the muscle cell. This action potential propagates along the long, thin muscle cell—in the same way that the neuron action potential moves along nerve fibers—and triggers contraction of the muscle cell. This chapter will begin by examining the events that intervene between the occurrence of the action potential in the plasma membrane of the muscle cell and the activation of the contraction: the process of **excitation–contraction coupling.** We will then consider the organization of the motor nervous system and how it integrates the twitch-like contractions of individual muscle fibers into the smooth and graded contractions of a muscle as a whole.

EXCITATION–CONTRACTION COUPLING IN SKELETAL MUSCLE

The three types of muscle

The body contains two general classes of muscle: striated and smooth. Both are named for the characteristic appearance of the individual cells making up the muscle tissue when viewed through a microscope. **Striated muscle cells** (Fig. 9.1) exhibit closely spaced, crosswise stripes (striations); **smooth muscle cells** do not and thus have a smooth appearance. Smooth muscle is found in the gut, blood vessels, uterus, and other locations in which contractions are usually slow and maintained. In contrast, the muscles that move and support the skeletal framework of the body—the skeletal muscles—consist of striated muscle cells. This chapter will focus on the structure and properties of these cells.

The cells that make up the muscle of the heart are also striated. Because the membranes of these cells are electrically quite different from those of skeletal muscle cells, **cardiac muscle** is usually regarded as a distinct class in its own right. (The characteristics of cardiac muscle will be discussed in chapter 13.)

STRUCTURE OF SKELETAL MUSCLE

Figure 9.1 shows the structure of a typical mammalian skeletal muscle at progressively greater magnification. To the naked eye, an intact muscle appears to be vaguely striped longitudinally (see Fig. 9.1A). Upon closer

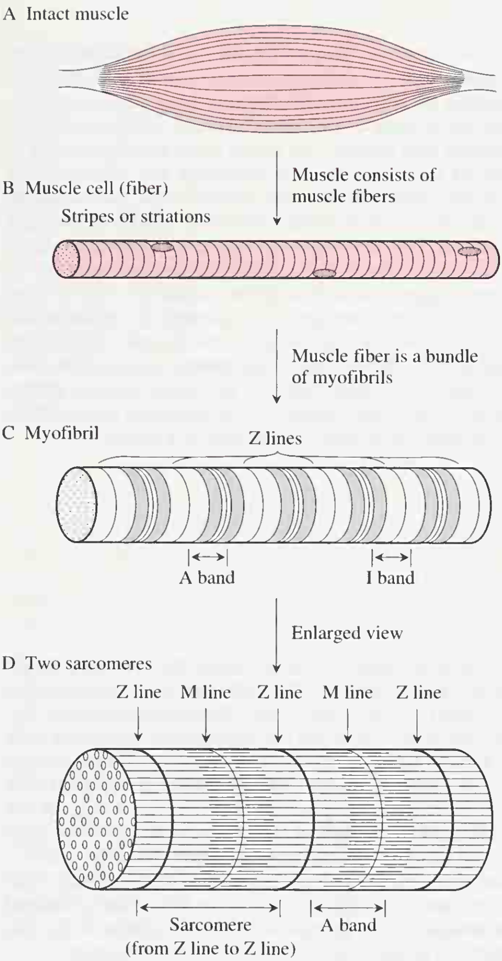


Figure 9.1
The microscopic structure of a skeletal muscle. Muscle components are viewed at increasing magnification in A through D.

inspection, it becomes apparent that the muscle consists of bundles of individual cells: the muscle cells or muscle fibers (see Fig. 9.1B). In mammalian muscle, each cell is approximately 50 μm in diameter and is typically as long as the entire muscle. Thus, muscle cells are long, thin fibers. Because the end-plate region extends over only a few microns, a rapidly propagating action potential—like that of a nerve cell—is required in skeletal muscle cells to pass along the motor neuron's command to contract.

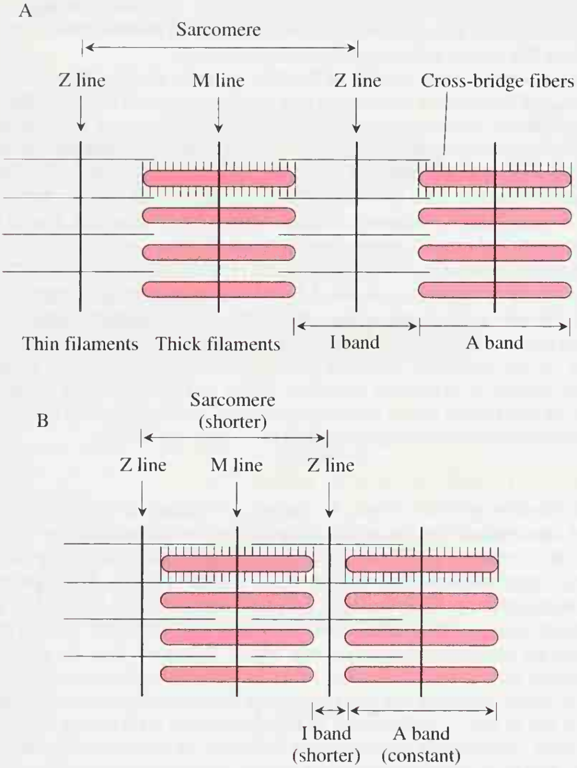
Individual muscle cells consist of bundles of even smaller fibers called **myofibrils**, and the plasma membrane of a single muscle cell encloses many of these myofibrils. At the level of the myofibrils, the structural basis of the crosswise striations of skeletal muscle cells begins to become apparent. Myofibrils exhibit a repeating pattern of crosswise light and dark stripes (see Fig. 9.1C). Early anatomists who first described these stripes had no idea of their function and gave them the names A band, I band, and Z line. The I band is a predominantly light region with a dark Z line at its center, while the A band is a darker region separating two I bands of the repeating pattern. At a higher magnification, it is apparent that the A band has its own internal structure (see Fig. 9.1D); two darker areas at the outer edges of the A band are separated by a lighter region with a faint dark line, called the M line, at the center. The basic unit of the repeating striation pattern of a myofibril, called a **sarcomere**, is defined as extending from one Z line to the next—that is, from the center of one I band to the center of the next I band. Figure 9.1D shows two complete sarcomeres along the length of a single myofibril.

Changes in striation pattern on contraction

Myofibril striation patterns might be rather uninteresting except for the important observation that the relationship among the stripes changes when a muscle cell contracts. This change can be best appreciated at the level of the electron microscope, as shown in the diagram in Figure 9.2. Through the electron microscope, a myofibril can be seen to consist of two kinds of longitudinally oriented filaments, called thick and thin filaments. Both types of filaments are arrayed in parallel groups. Figure 9.2 shows that the parallel thin filaments are connected to each other by perpendicular cross connections at the Z line. Similarly, the thick filaments within a sarcomere are joined together at the M line. A comparison of Figures 9.2 and 9.1D shows that the lighter I band corresponds to the region occupied by only thin filaments, while the darker A band corresponds to the spatial extent of the thick filaments. The darker regions at the two edges of the A band correspond to the region where the thick and thin filaments overlap. The thick filaments bear thin appendages that appear to link to the thin filaments in this region of overlap, forming **cross bridges** between the thick and thin filaments.

Upon contraction, the length of each sarcomere shortens—that is, the distance between successive Z lines diminishes. The width of the A band remains constant during contraction, and only the I band becomes shorter when the muscle contracts. In terms of the thick and thin filaments, this observation can be explained by the **sliding filament hypothesis** (see Fig. 9.2B). Neither the thick filaments nor the thin filaments change in length during a contraction. Instead, shortening occurs because the filaments slide

Figure 9.2
A schematic representation of the relationships between thick and thin filaments of a myofibril in (A) a relaxed muscle and (B) a contracted muscle.



with respect to one another, thereby increasing the region of overlap. To understand how this sliding occurs, we must examine the molecular makeup of the thick and thin filaments.

Molecular composition of filaments

The thick filaments are aggregates of a protein called **myosin**, which consists of a long fibrous "tail" connected to a globular "head" region, as shown schematically in Figure 9.3. The fibrous tails tend to aggregate into long filaments, with the heads projecting off to the side. Figure 9.4 shows a generally accepted view of the arrangement of myosin molecules in the thick filaments of a sarcomere. The aggregated tails form the backbone of the thick filament, and the globular heads form the cross bridges that connect with adjacent thin filaments.

The globular head of myosin contains a region that can bind adenosine triphosphate (ATP) and split one of the high-energy phosphate bonds of the ATP, releasing the stored chemical energy. In this way, myosin acts as an ATPase. The energy provided by the ATP is transferred to the myosin molecule, which is transformed into an "energized" state. This sequence can be summarized as follows:

Myosin + ATP → Myosin • ATP → Energized Myosin • ADP + Pi

In this equation, the dot indicates that two molecules are bound together, as in an enzyme–substrate complex. To make a mechanical analogy, the globular head behaves as if it were attached to the fibrous tail at a hinged connection point. The energy released by ATP causes the head to pivot around the hinge and enter an energized state (Fig. 9.5). To continue with mechanical analogies, this action can be envisioned as cocking the spring-loaded hammer of a cap pistol. As we will see shortly, the energy stored in this energized form of myosin fuels the sliding of the filaments during contraction.

The thin filaments within a myofibril largely consist of the protein **actin.** Thin filaments also contain two other kinds of protein molecules, **troponin** and **tropomyosin.** (The roles of troponin and tropomyosin in contraction will be discussed later.) Actin is a globular protein that polymerizes to form long chains. Consequently, the thin filament can be thought of as a long

Figure 9.3
A diagram of the structure of a single molecule of the thick-filament protein, myosin. The fibrous tail is connected to the globular head region via a flexible connection point. The globular head includes a region that can bind and split a molecule of ATP.

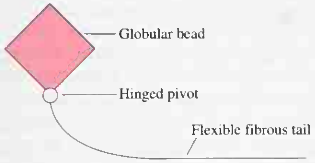
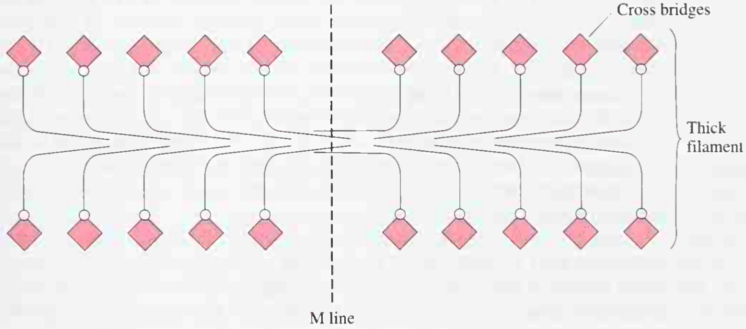
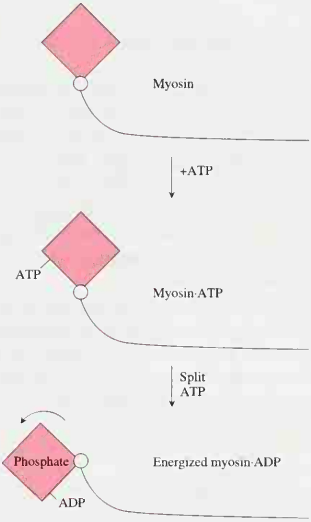


Figure 9.4
The hypothetical structure of a thick filament. The fibrous tails of individual myosin molecules polymerize to form the backbone of the filament. The globular heads radiate perpendicular to the long axis of the filament to form the cross bridges to the thin filament. The myosin molecules reverse orientation at the M line.



string of actin molecules, much like a pearl necklace. (Actually, each thin filament consists of two actin chains entwined about one another in a helix. For a conceptual understanding of the sliding filament hypothesis, however, the simpler model will suffice.) Each actin molecule in the chain contains a binding site that can combine with a specific site on the globular head of a myosin molecule. This location provides the site of attachment for the cross bridge on the thin filament.

Figure 9.5
A molecule of myosin can bind a molecule of ATP. Energy released by splitting a high-energy phosphate bond of the ATP is used to form an energized form of myosin. The transition from resting to energized state involves rotation of the globular head about its flexible attachment site to the fibrous tail.



Interaction between myosin and actin

When actin combines with energized myosin, the stored energy in the myosin molecule is released. The myosin molecule then returns to its resting state, and the globular head pivots about its hinged attachment point to the thick filament. The pivoting motion requires that the thick and thin filaments move longitudinally with respect to one another, as illustrated in Figure 9.6. Although the exact nature of the chemical changes in a myosin molecule during the transition from resting to energized state, and back again, remains unknown, the sliding filament hypothesis requires some chemical equivalent of the hinged arrangement shown in Figure 9.6.

How is the bond between actin and myosin broken so that a new cycle of sliding may begin? In the scheme presented so far, each myosin molecule on the thick filament could interact only once with an actin molecule on the thin filament, and the total excursion of sliding would be restricted to that produced by a single pivoting of the globular head. To produce the large filament movements that actually occur, the attachment of the cross bridges must be broken so that the cycle of myosin energization, binding to actin, and movement can be repeated.

This full cycle is summarized in Figure 9.7. When energized myosin binds to actin and releases its stored energy, it releases the ADP bound to the ATPase site of the globular head. A new molecule of ATP can then bind to the myosin. Binding of ATP induces the bond between actin and myosin to break, possibly because of structural changes in the globular head induced by the interaction between ATP and myosin. The new ATP molecule is then split by myosin and regenerates the energized form, which is free to interact with another actin molecule on the chain constituting the thin filament. Note that ATP has two functions in this scheme: it provides the energy to "cock" myosin for movement, and it breaks the interaction between actin and myosin after movement has occurred. If ATP is absent, then actin and myosin become stuck together and a rigid muscle results (as in rigor mortis).

Each of the many myosin heads on an individual thick filament independently goes through repetitive cycles of energization by ATP, binding to actin, release of stored energy to produce sliding, and detachment from actin. Each cycle splits one molecule of ATP into ADP and inorganic phosphate.

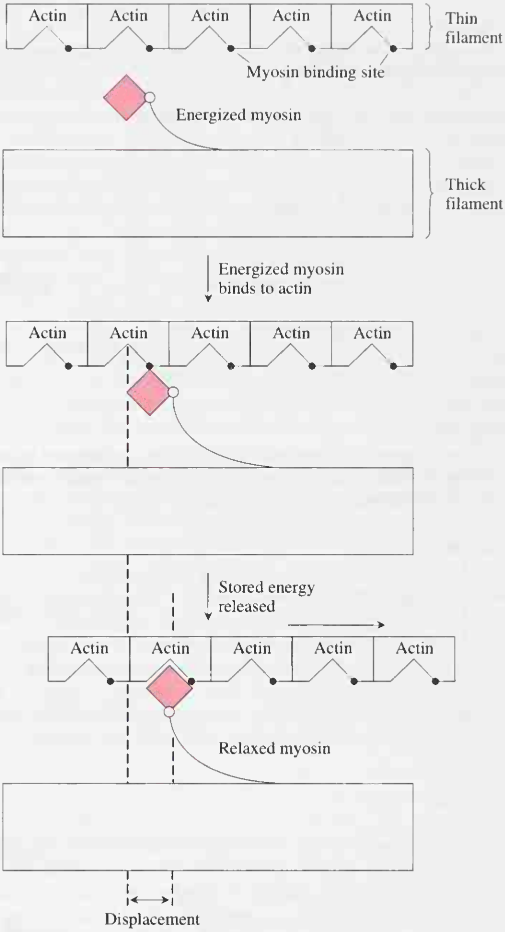


Figure 9.6
A schematic representation of the interaction between energized myosin and actin based on the sliding filament hypothesis. Energized myosin binds to a specific binding site on actin, releasing the stored energy. The resulting relaxation of the myosin molecule entails rotation about the flexible attachment site to the rest of the thick filament. The rotation induces longitudinal sliding of the filaments. The fibrous tail connecting the myosin molecule to the rest of the thick filament is "springy," permitting the globular head to reach across to the cross-bridge attachment site on the thin filament.

The orientation of the myosin heads reverses at the midpoint of the thick filament, the M line (see Fig. 9.4), providing the proper orientation to pull both Z lines at the boundary of a sarcomere toward the center (Fig. 9.8). The thin filaments attached to the left Z line will be pulled to the right by the cyclical pivoting of the myosin cross bridges. Similarly, the thin filaments attached to the right Z line will be pulled to the left. Thus, each sarcomere in each myofibril shortens, as does the muscle as a whole.

Figure 9.7
The cycle of cross-bridge formation and dissociation between myosin and actin during filament sliding.

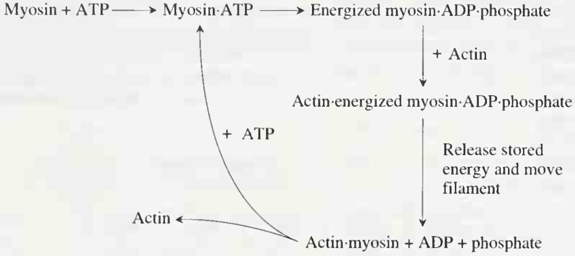
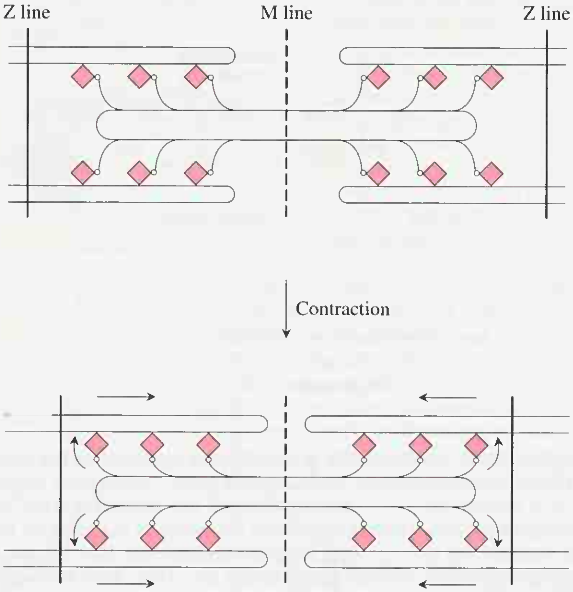

Myosin + ATP
Myosin·ATP
Energized myosin·ADP·phosphate
+ Actin
Actin·energized myosin·ADP·phosphate
Release stored energy and move filament
Actin·myosin + ADP + phosphate
Actin
+ ATP

Figure 9.8
The mechanism of sarcomere shortening during contraction based on the sliding filament hypothesis. For clarity, the myosin heads are shown acting in concert, although they behave independently in reality.



REGULATION OF CONTRACTION

The scheme summarized in Figure 9.7 does not include a mechanism to control the interaction between actin and myosin. As long as ATP is present, we would therefore expect every muscle in the body to exist in a perpetual state of maximum contraction. This section will examine the molecular mechanisms that prevent the interaction of actin with myosin except when a contraction is triggered by an action potential in the muscle cell membrane.

Recall that thin filaments contain the proteins troponin and tropomyosin. These proteins are responsible for regulating the interaction between individual myosin and actin molecules in the thick and thin filaments. The regulatory scheme is summarized in Figure 9.9. In the resting muscle, tropomyosin's position on the thin filament allows it to effectively cover the myosin binding site on actin. In this way, tropomyosin blocks myosin's access to the binding site. The position of tropomyosin on the actin polymer is in turn regulated by troponin. In the resting state, troponin locks tropomyosin in the blocking position. Thus, tropomyosin acts like a trapdoor covering the myosin binding site, and troponin acts like a lock to keep the door from opening.

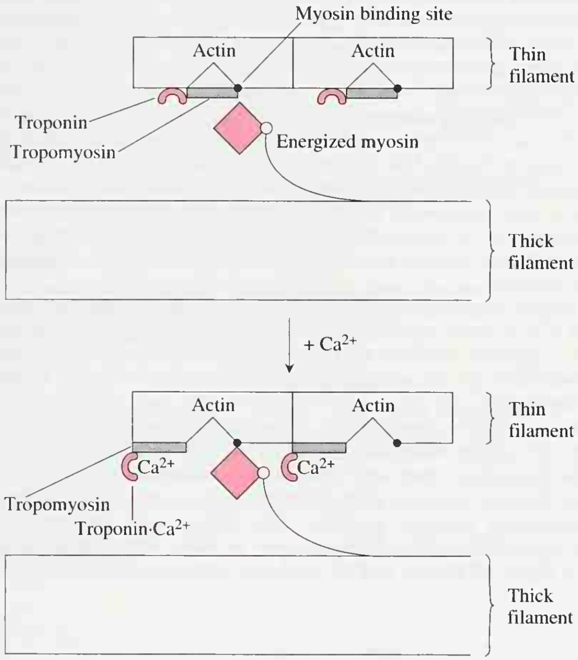
What triggers tropomyosin to reveal the myosin binding sites on actin? The signal that initiates contraction is the binding of calcium ions to troponin. Each troponin molecule contains a specific binding site for a single calcium ion. Normally, the concentration of calcium inside the cell is very low, and the binding site remains unoccupied. In this state, troponin locks tropomyosin in the blocking position. When an action potential occurs in the muscle cell plasma membrane, however, the concentration of calcium ions in the intracellular fluid rises dramatically, and calcium binds to troponin. The troponin molecule then undergoes a structural change, and the altered interaction between troponin and tropomyosin prompts tropomyosin to uncover the myosin binding site on actin. The cycle of events depicted in Figure 9.7 begins, and the filaments slide past one another.

The sarcoplasmic reticulum

What is the origin of the calcium that triggers the interaction of actin and myosin underlying the sliding of the filaments? Recall from chapter 7 that a rise in internal calcium initiates the release of chemical transmitters during synaptic transmission. In that case, the calcium enters the cell from the ECF through voltage-sensitive calcium channels in the plasma membrane. In the case of skeletal muscle, however, the calcium does not come from outside the cell; rather, it is injected into the ICF from a separate intracellular compartment called the **sarcoplasmic reticulum.** The sarcoplasmic reticulum is an intracellular sack that surrounds the myofibrils of a muscle cell. It forms a separate intracellular compartment, bounded by its own membrane, which is not continuous with the plasma membrane of the muscle cell.

The concentration of calcium ions inside the sarcoplasmic reticulum is much higher than in the rest of the intracellular space; in fact, it probably

Figure 9.9
The regulation of the interaction between actin and myosin by calcium ions, troponin, and tropomyosin. In the absence of calcium ions, tropomyosin blocks access to the myosin binding site of actin. When calcium binds to troponin, the binding site becomes accessible and the sliding interaction is allowed.



exceeds the concentration of calcium in the ECF. This accumulation of calcium is accomplished by a calcium pump in the membrane of the sarcoplasmic reticulum. Like the sodium pump of the plasma membrane, this calcium pump uses metabolic energy in the form of ATP to transport calcium ions across the membrane against a large concentration gradient—in this case, moving calcium ions into the sarcoplasmic reticulum. To initiate a contraction, a puff of calcium ions is released from the sarcoplasmic reticulum, which is strategically located surrounding the contractile apparatus of the myofibrils. The action of the released calcium ends when the ions are pumped back into the sarcoplasmic reticulum by the calcium pump. Thus, ATP plays a third role in the contraction process: as the fuel for the calcium pump, it is responsible for terminating a contraction.

Calcium is released from the sarcoplasmic reticulum via calcium-selective ion channels that are located in the sarcoplasmic reticulum membrane. These calcium channels differ dramatically from the voltage-dependent calcium channels we encountered in our discussion of synaptic transmission. Rather than being activated by depolarization, the calcium channels in the sarcoplasmic reticulum are activated by an increase in cytoplasmic calcium concentration. For this reason, they are known as **calcium-induced calcium-release channels.** If calcium is released from the sarcoplasmic reticulum via channels that are themselves activated by a calcium increase, then the calcium-release process exhibits positive feedback reminiscent of the rising phase of the action potential (where depolarization opens sodium channels, which in turn produce further depolarization). This approach ensures that calcium release takes place rapidly, producing fast and complete activation of the contraction mechanism.

The transverse tubule system

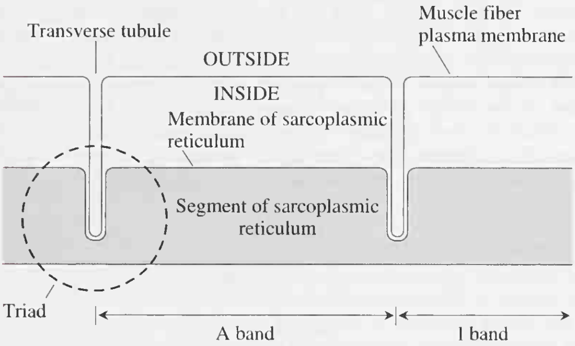
How does an action potential in the plasma membrane of a muscle cell trigger the release of calcium from the sarcoplasmic reticulum? The crucial aspect of the action potential in triggering contraction is depolarization of the plasma membrane; any manipulation that produces depolarization can cause contraction.

How can depolarization of the plasma membrane at the outer surface of the cell affect the sarcoplasmic reticulum surrounding myofibrils deep in the interior of the muscle cell? Periodic infoldings, or invaginations, of the plasma membrane extend into the depths of the muscle fiber; these invaginations are called the **transverse tubule system** (Fig. 9.10). The long fingers of the transverse tubules provide a path for depolarization that results from an action potential in the surface membrane to spread to the cell interior and influence events deep within the cell.

In most animal species, the transverse tubules are located at the boundary between the A band and the I band. At locations where the tubules encounter the sarcoplasmic reticulum as they project into the muscle cell, the membranes of the two structures come into close apposition to form a structure called a **triad.** The triad presumably represents the point of interaction between the depolarizing signal that is spreading along the transverse tubule and the membrane of the sarcoplasmic reticulum. Note, however, that although the membranes are close together at a triad, they do not touch. This lack of continuity means that the depolarization produced during the action potential cannot spread directly to the sarcoplasmic reticulum. Therefore, some indirect signal is required to link depolarization of the transverse tubule to calcium release by the sarcoplasmic reticulum.

Because calcium release from the sarcoplasmic reticulum is mediated via channels that are themselves activated by an increase in cytoplasmic calcium concentration, it is natural to suppose that the link between transverse tubules and sarcoplasmic reticulum is mediated by an influx of calcium ions

Figure 9.10
The transverse tubules are invaginations of the plasma membrane of the muscle fiber. Depolarization during an action potential can spread along the transverse tubules to the interior of the fiber. The triad—a region where the membranes of the tubule and the sarcoplasmic reticulum come into close proximity—presumably represents the area where depolarization acts to release calcium from the sarcoplasmic reticulum.


Transverse tubule
Muscle fiber plasma membrane
OUTSIDE
INSIDE
Membrane of sarcoplasmic reticulum
Segment of sarcoplasmic reticulum
Triad
A band
I band

from the extracellular space. Indeed, the membrane of the transverse tubules contains voltage-dependent calcium channels that are opened by depolarization, and these ion channels are required for the initiation of contraction. In cardiac muscle, for example, influx of calcium from the ECF via these depolarization-activated calcium channels is required to initiate the muscle contraction. Thus, calcium ions through the transverse tubule calcium channels actually trigger the calcium release from the sarcoplasmic reticulum in cardiac muscle cells.

In skeletal muscle, however, calcium influx via the calcium channels of the transverse tubules is not required to trigger contraction, and some other linkage mechanism is needed. Although this mechanism is not yet fully understood, the calcium channels of the transverse tubule are believed to act as voltage sensors that detect the depolarization produced by the action potential. A direct physical link, extending through the intracellular space, is thought to connect single calcium-induced calcium-release channels in the sarcoplasmic reticulum membrane to single voltage-dependent calcium channels in the immediately adjacent membrane of the transverse tubule. Perhaps conformation changes in the transverse tubule calcium channel upon depolarization induce conformation changes in the calcium-induced calcium-release channels via this physical linkage. These changes might then cause the local release of calcium from the sarcoplasmic reticulum, initiating the explosive calcium-induced release of calcium from the sarcoplasmic reticulum as a whole.

SUMMARY OF EXCITATION–CONTRACTION COUPLING

The sequence of events leading to contraction of a skeletal muscle fiber after stimulation of its motor neuron can be summarized as follows:

1. Acetylcholine released from the presynaptic terminal depolarizes the end-plate region of the muscle fiber.
2. The depolarization initiates an all-or-nothing action potential in the muscle fiber, which propagates along the entire length of the fiber.
3. Depolarization produced by the action potential spreads to the interior of the fiber along the transverse tubule system.
4. Depolarization of the transverse tubules causes release of calcium ions by the sarcoplasmic reticulum.
5. Released calcium ions bind to troponin molecules on the thin filaments.
6. When calcium combines with troponin, tropomyosin uncovers the myosin binding site of actin.
7. Globular heads of myosin molecules, which have been energized by splitting a high-energy phosphate bond of ATP, attach to actin at the uncovered binding site.
8. The stored energy of the activated myosin is released and propels the thick and thin filaments past each other. The spent ADP is then released from myosin.
9. A new ATP binds to myosin, breaking its attachment to the actin molecule.
10. The new ATP is split to reenergize myosin and return the contraction cycle to step 7.
11. Contraction is maintained as long as internal calcium concentration remains elevated. The calcium concentration declines as calcium ions return to the sarcoplasmic reticulum via an ATP-dependent calcium pump.

CONTRACTION OF WHOLE MUSCLE

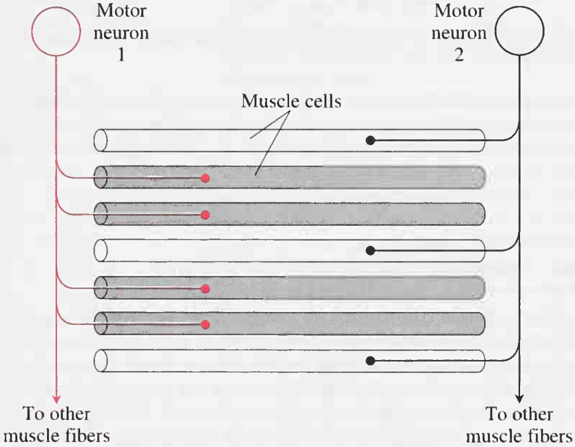
Up to this point, we have been concerned with the physiology of muscle at the level of single muscle fibers. We have achieved some understanding of the mechanisms involved in the linkage between an action potential in a presynaptic motor neuron and the contraction of the postsynaptic muscle cell. The motor neuron depolarizes the muscle fiber, causing an action potential that, in turn, triggers the all-or-nothing contraction of the fiber.

We will now step back from this cellular perspective and look at the functioning of a skeletal muscle as a whole. The following discussion focuses on how the all-or-nothing twitches of single muscle fibers become integrated to produce smooth, graded movements.

THE MOTOR UNIT

A single motor neuron makes synaptic contact with a number of muscle fibers. The actual number varies considerably from one muscle to another, and from one motor neuron to another within the same muscle; a single motor neuron may contact as few as 10 to 20 muscle fibers or more than 1000. In mammals, a single muscle fiber normally receives synaptic contact from only one motor neuron. Therefore, a single motor neuron and the muscle fibers to which it is connected form a basic unit of motor organization called the **motor unit** (Fig. 9.11). Recall from chapter 7 that the synapse between a motor neuron and a muscle fiber is a one-for-one synapse—that is, a single presynaptic action potential produces a single postsynaptic action potential and hence a single twitch of the muscle cell. As a result, all muscle cells in a motor unit contract together. Consequently, the fundamental unit

Figure 9.11
A schematic illustration of the innervation of a small number of muscle fibers in a muscle. The shaded muscle fibers form part of the motor unit of motor neuron 1; the unshaded fibers form part of the motor unit of motor neuron 2.



of contraction of the whole muscle is not the contraction of a single muscle fiber, but rather the contraction produced by all muscle cells included in the motor unit.

Gradation in the overall strength with which a particular muscle contracts lies under the control of the nervous system. The nervous system accomplishes this task via two basic methods:

- Variation in the total number of motor neurons activated, and hence in the total number of motor units contracting.
- Variation in the frequency of action potentials in the motor neuron of a single motor unit.

The greater the number of motor units activated, the greater the strength of contraction. Similarly, but within limits, the greater the rate of action potentials within a motor unit, the greater the strength of the resulting summed contraction.

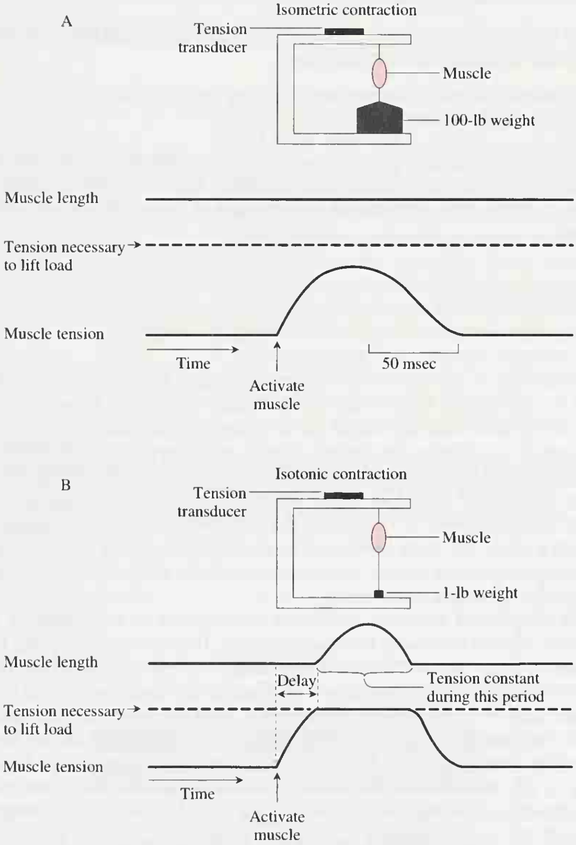
THE MECHANICS OF CONTRACTION

Upon stimulation of the nerve controlling a muscle, the resulting action potentials in the muscle fibers initiate the sliding interaction between the filaments of the individual myofibrils in the muscle. This sliding generates a force that tends to shorten the muscle fibers, and hence the muscle as a whole. Whether the muscle actually shortens, however, depends on the load attached to the muscle. While we might attempt to order the muscles in our arms to lift an automobile, it is unlikely that they would be able to shorten against such a load. The force developed in an activated muscle is called the muscle **tension**, and the muscle will shorten and lift the load only if the tension equals the weight of the load.

We can distinguish between two kinds of response to activation of a muscle. If the muscle tension is less than the load, the contraction is said to be **isometric** ("same length") because the length of the muscle does not change even though the tension increases. That is, the force exerted on the load by the muscle is insufficient to move the load, so the muscle cannot shorten. In the isometric contraction diagrammed in Figure 9.12A, an isolated muscle is attached to a load it cannot lift. The tension that results from activation of the muscle is registered by a strain gauge that measures the minuscule flexing of the rigid strut to which the muscle is attached. A single activation of the muscle triggers a transient increase in tension, typically lasting about 0.1 s. You can easily feel the tension developed in an isometric contraction by placing your palms together with your arms flexed in front of your chest and pushing with both hands, one against the other.

If the tension is great enough to overcome the weight of the load, the contraction is said to be **isotonic** ("same tension") because the tension remains constant once it reaches the level necessary to move the load. In Figure 9.12B, the strain gauge again records the increase in tension, as with

Figure 9.12
Measurements of muscle length and muscle tension during (A) isometric and (B) isotonic contractions. At the upward arrow, the nerve innervating the muscle is stimulated, thereby activating the muscle fibers.



the isometric contraction. When the tension reaches the threshold necessary to lift the load, it levels off and the muscle begins to shorten as the load is lifted. During the change in muscle length, the tension remains constant and equal to the weight of the load; this weight—hanging from the muscle and support strut—determines the flexing measured by the strain gauge. In an isotonic contraction, the force developed by the sliding filaments in the myofibrils making up the muscle produces work in the form of moving the load through space.

One difference between isometric and isotonic contractions is observed in the delays noted between muscle activation and the occurrence of a measurable change in either muscle tension (isometric) or muscle length (isotonic). The tension begins to rise within a few milliseconds, which is the time required for the effect of the excitation–contraction process to take hold. If muscle length is measured, however, a pronounced delay is observed between activation of the muscle and beginning of shortening. This delay represents the time required for the tension to rise to the point where the load is lifted, and it depends on the size of the load. The shortening begins quickly with light loads, but its onset is progressively delayed with heavier loads. With sufficiently heavy loads, no shortening will be observed and the contraction will become isometric. In addition, with heavier loads the duration of shortening will be less and the maximum speed of shortening will be slower. In a sense, the measurement of tension during an isometric contraction gives a more direct view of the contractile state of the muscle; for this reason, subsequent examples in this chapter will focus on isometric contractions.

The relationship between isometric tension and muscle length

How does the tension developed in a muscle relate to the microscopic contractile apparatus within each muscle cell and to the sliding-filament mechanism discussed earlier in this chapter? To answer this, we will consider the relationship between the magnitude of isometric tension developed by a muscle and the muscle length at which the tension is measured. Suppose the experiment diagrammed in Figure 9.12A were repeated at a variety of muscle lengths, as set by varying the distance between the upper support bar and the weight. As the muscle is stretched beyond its normal resting length, the tension developed upon stimulating the muscle would fall off rapidly, reaching zero at approximately 175% of resting length. This is shown in Figure 9.13A, in which peak isometric tension is plotted against muscle length (expressed as a percentage of the resting length of the unstimulated muscle). Such behavior can be understood in terms of the underlying state of the thick and thin filaments constituting each sarcomere. As the distance between Z lines increases, the degree of overlap between thick and thin filaments declines, and thus the number of myosin head groups available to form cross bridges diminishes. Finally, with sufficient stretch, no overlap occurs (Fig. 9.13B, number 3) and no tension is possible.

If the muscle is artificially shortened, isometric tension also declines, falling to zero at approximately 50% of resting length. This effect appears as the distance between successive Z lines becomes sufficiently short so that the thin filaments attached to one Z line overlap with the thin filaments attached to the neighboring Z line (see Fig. 9.13B, number 1). This overlap distorts the necessary spatial relation between thin and thick filaments required for cross-bridge attachments to form, once again leaving fewer cross

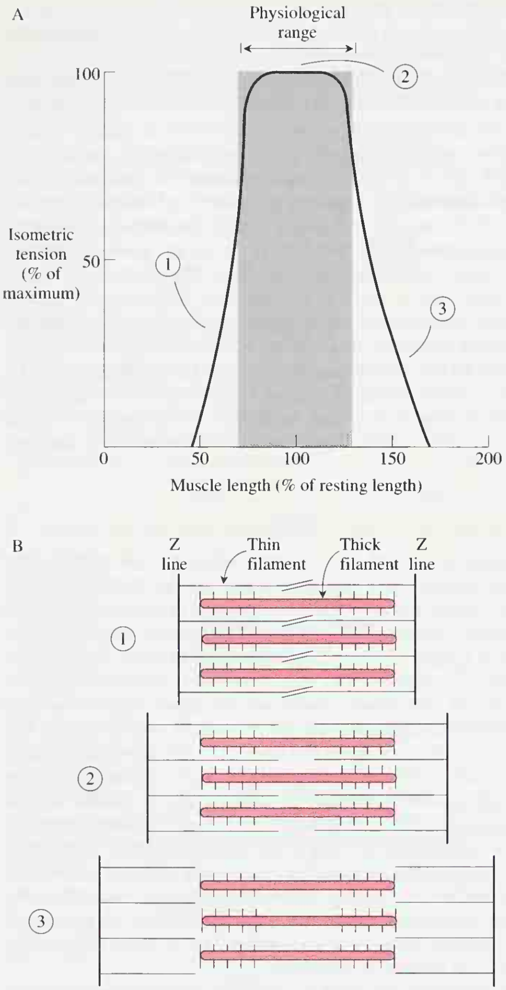


Figure 9.13
The relationship between muscle length and strength of isometric tension. The graph in A shows the isometric tension developed when a muscle is stimulated, plotted as a function of the length of the muscle. Tension is expressed as a percentage of the maximum tension, and muscle length is expressed as a percentage of resting length. The shaded area shows the range of muscle length over which the muscle would actually operate in the body. The diagrams in B show the states of the thick and thin filaments within a sarcomere at the three numbered positions marked in A.

bridges available to develop tension. In addition to this geometrical effect, other factors (such as reduced coupling between depolarization of the membrane and release of calcium from the sarcoplasmic reticulum) might contribute to the reduced peak tension at short muscle lengths.

The drop in tension with both increasing and decreasing length means that an optimal range of length exists for development of tension; within this range, there is maximal overlap of thin filaments with the cross bridges of the thick filaments (see Fig. 9.13B, number 2). For maximum efficiency, the range of length over which a muscle operates should be close to this optimal range. This is in fact the case—the length of a functioning skeletal muscle in the body remains within about 30% of the optimal length (the shaded region in Figure 9.13A). To ensure that this range is not exceeded, precise arrangements of muscle-fiber length, tendon length and attachment sites, and joint geometry have evolved that are appropriate for the functional task of each muscle.

CONTROL OF MUSCLE TENSION BY THE NERVOUS SYSTEM

Recruitment of motor neurons

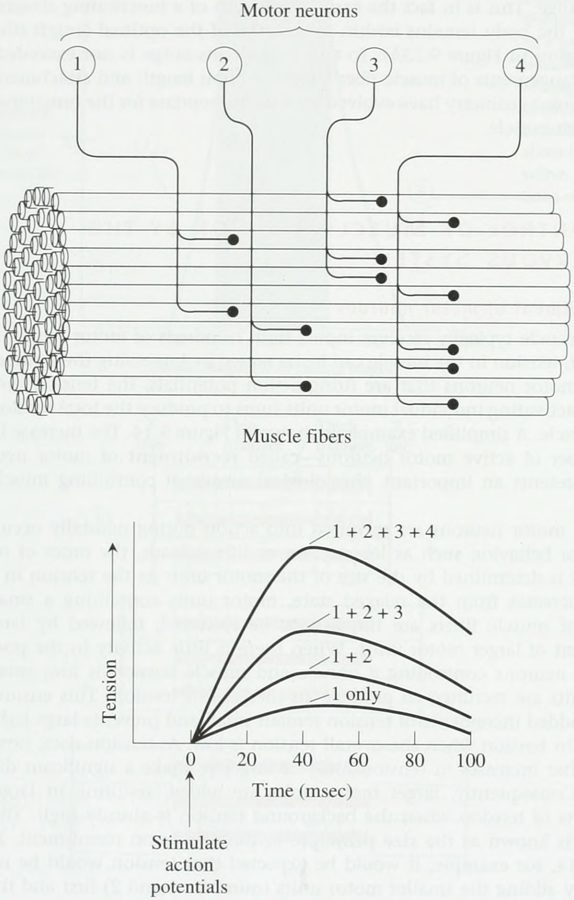
A single muscle typically receives inputs from hundreds of motor neurons. As a result, tension in the muscle can be increased by increasing the number of these motor neurons that are firing action potentials; the tension produced by activating individual motor units sums to produce the total tension in the muscle. A simplified example is shown in Figure 9.14. The increase in the number of active motor neurons—called **recruitment** of motor neurons—represents an important physiological means of controlling muscle tension.

When motor neurons are recruited into action during naturally occurring motor behavior, such as locomotion or lifting loads, the order of recruitment is determined by the size of the motor unit. As the tension in a muscle increases from the relaxed state, motor units containing a small number of muscle fibers are the first to be recruited, followed by later recruitment of larger motor units. When there is little activity in the pool of motor neurons controlling a muscle and muscle tension is low, small motor units are recruited to produce an increase in tension. This ensures that the added increments of tension remain small and prevents large jerky increases in tension when the overall tension is low. As tension rises, however, further increases in tension must be larger to make a significant difference. Consequently, larger motor units are added, resulting in larger increments of tension when the background tension is already high. This behavior is known as the **size principle** in motor neuron recruitment. In Figure 9.14, for example, it would be expected that tension would be increased by adding the smaller motor units (numbers 1 and 2) first and the largest unit (number 4) last.

Fast and slow muscle fibers

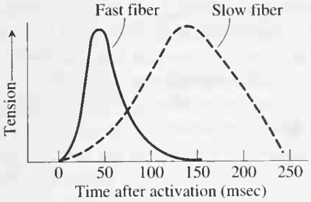
The time delay between the occurrence of the action potential in a muscle cell and the peak of the resulting tension is not constant across all muscle

Figure 9.14
A simple muscle consisting of four motor units of varying size. The graph below shows isometric tension in response to simultaneous action potentials (at the arrow) in various combinations of the motor neurons.



fibers. The delay to peak tension can be as short as 10 ms or as long as 200 ms. In general, muscle fibers can be grouped into two classes—fast and slow—on the basis of this speed. Figure 9.15 provides samples of isometric contractions in fast and slow fibers. Both slow and fast fibers are found in most muscles, but slow fibers predominate in muscles that must maintain steady contraction, such as those involved in keeping the human body standing upright. Fast muscle fibers are more common in muscles that require rapid contraction, such as those involved in jumping and running. The fastest muscle fibers are those of muscles that move the eyes in rapid jumps, like the movements made by your eyes as you scan the words on this page.

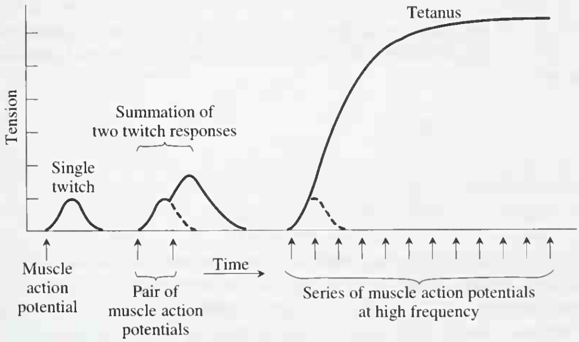
Figure 9.15
A comparison of speed of development of isometric tension in fast and slow muscle fibers.



Temporal summation of contractions within a single motor unit

When motor neurons are activated during naturally occurring movement, they do not typically fire just a single action potential. Instead, action potentials tend to occur in bursts or as steady discharges emitted at a relatively constant rate. In many cases, action potentials within a burst will be separated by only 10 ms or less. Under normal conditions, each of these many action potentials in a motor neuron will produce a corresponding action potential in each of the motor unit's muscle fibers. Because the tension resulting from a single action potential typically lasts for many tens or hundreds of milliseconds, considerable opportunity exists for the effects of succeeding muscle action potentials in a series to be summed (Fig. 9.16).

Figure 9.16
Isometric tension in response to a series of action potentials in a muscle. The dashed lines show the expected response if only the first action potential of a series occurred.



Such temporal summation of individual twitches represents a major strategy by which the nervous system controls tension in skeletal muscles.

The amount of summation within a burst of muscle action potentials depends on the frequency of action potentials: the higher the frequency, the greater the resulting summed tension. When the frequency is sufficiently high, however, the individual tension responses of the muscle fuse together into a plateau of tension (see Fig. 9.16). Further increase in frequency beyond this point does not increase tension, because the muscle has reached its maximum response. This plateau state is called **tetanus.** As expected from the examples shown in Figure 9.15, the frequency of stimulation required to produce tetanus varies considerably depending on whether slow or fast fibers are involved. A frequency of more than 100 action potentials per second may be required for fast fibers, while a frequency of 20 action potentials per second may suffice for slow fibers.

Asynchronous activation of motor units during maintained contraction

As anyone who has performed physical labor for long periods of time or who has exercised vigorously can attest, muscle contractions cannot be maintained indefinitely—muscles fatigue and must be rested. Thus, the state of tetanus (see Fig. 9.16) could not be maintained in a single motor unit for very long without allowing the muscle fibers in the motor unit to relax. Some muscles—such as those involved in maintaining body posture—must contract for prolonged periods, however. What mechanism helps prevent muscle fatigue during these prolonged contractions?

When tension is maintained in a muscle, not all motor neurons to the muscle are active simultaneously. The activity of the motor units occurs in bursts separated by quiet periods, with the activity of different motor units being staggered in time. An example of this kind of asynchronous activity during steady contraction is shown in Figure 9.17. In the figure, the summation of the tensions produced by the activity of only three motor units (each active only half of the time) gives a reasonably smooth, steady tension. With hundreds of motor units available in many muscles, a much smoother and larger steady tension could be maintained with less effort on the part of any one motor unit. In this manner, asynchronous activation of motor neurons to a muscle permits a prolonged contraction with reduced fatigue of individual muscle motor units.

SUMMARY OF NEURAL CONTROL OF MUSCLE CONTRACTION

The basic unit of contraction of a skeletal muscle is the contraction of the group of muscle fibers making up a single motor unit, which consists of a single motor neuron and all muscle fibers receiving synaptic connections from that neuron. When the motor neuron fires an action potential, all

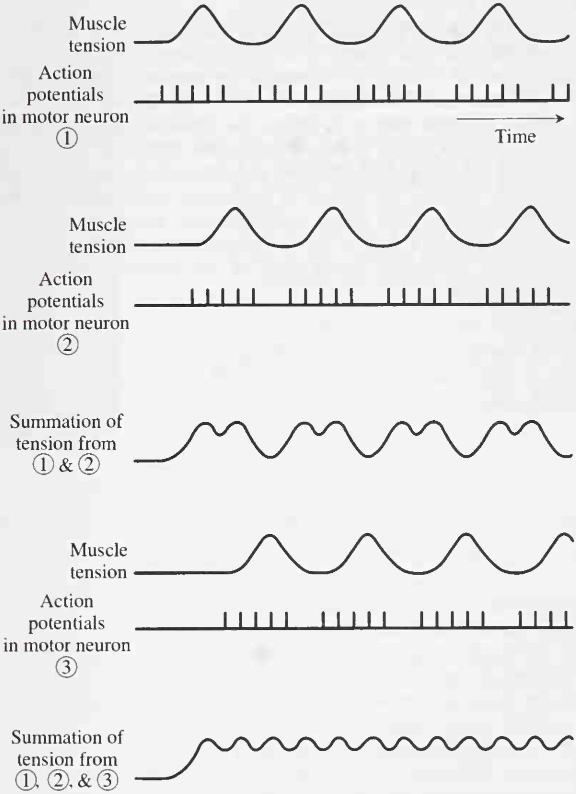


Figure 9.17
Summation of muscle tension during asynchronous activation of three motor units in a muscle.

Muscle tension
Action potentials in motor neuron ①
Time
Muscle tension
Action potentials in motor neuron ②
Summation of tension from ① & ②
Muscle tension
Action potentials in motor neuron ③
Summation of tension from ①, ②, & ③

muscle fibers in that motor unit twitch together. The magnitude of the contraction generated by activation of a motor unit depends on the number of muscle fibers in that motor unit. The number of fibers in a unit—and hence the magnitude of the tension produced by activation of the unit—varies considerably among the motor neurons innervating a particular muscle.

The type of contraction produced by activation of a whole muscle depends on the load against which the muscle is contracting. If the load is too great for the muscle to move, muscle length does not change during the contraction, which is then called an isometric contraction. If the tension is sufficient to overcome the weight of the load, the contraction will be accompanied by a shortening of the muscle. The tension in the muscle remains constant and equal to the weight of the load during shortening. Such a contraction is called an isotonic contraction.

The overall tension developed by a muscle depends on the number of motor units activated and the frequency of action potentials within a motor unit. Increasing muscle tension by increasing the number of active motor neurons is called motor neuron recruitment. When the frequency of action potentials within a motor unit is increased, the resulting muscle tension climbs until it reaches a steady plateau state, called tetanus. Normally, all motor neurons of a muscle are not active simultaneously during a maintained contraction; instead, the activity of individual motor neurons is restricted to periodic bursts that occur asynchronously among the pool of motor neurons controlling a muscle. This process helps reduce fatigue in the muscle by allowing individual motor units to rest periodically during a maintained contraction.

10

Spinal Cord Motor Mechanisms

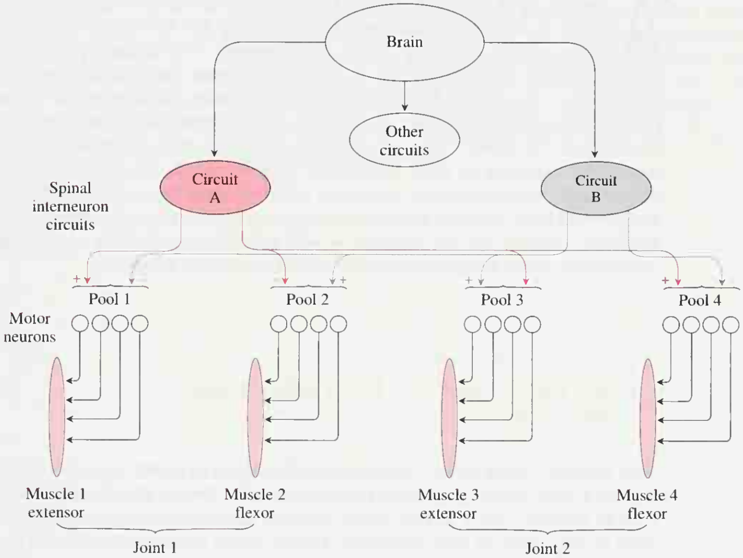
As we discussed in chapter 2, the hierarchical organization of the nervous system is one of the emergent trends during the evolution of increasingly complex forms of neural organization. This hierarchy is clearly visible in motor control systems. In complex nervous systems, such as those of mammals, the lowest level of the motor hierarchy consists of the spinal cord, which contains the final output neurons that must be activated to cause movement: the motor neurons. Similarly, in invertebrate nervous systems, the motor neurons of each segmental ganglion form the final common output path, which must be controlled by commands from other segmental ganglia and from cerebral ganglia to produce coordinated movements of the animal as a whole. In this chapter, we will examine some of the spinal cord circuits that serve as the building blocks for the motor hierarchy.

ADVANTAGES OF HIERARCHICAL MOTOR CONTROL

Each segment of the spinal cord includes thousands of motor neurons, which control a wide variety of different skeletal muscles. Even a simple movement, such as turning a page in this book, involves the careful temporal programming of excitation in large numbers of these motor neurons. If the brain had to select the precise timing of the firing of each motor neuron for each movement, the brain motor centers would need to carry out a massive computational effort. Instead, motor neurons are organized into larger functional units, or fundamental circuits, so that complex movements can be programmed by selecting from among a more manageable number of alternatives. These fundamental circuits dramatically reduce the number of possible choices for descending commands, restricting the alternatives to those that make functional sense for the particular set of muscles and joints controlled by a particular spinal segment.

Consider the simplified scheme diagrammed in Figure 10.1. Each of the four pools of motor neurons within the spinal cord segment controls a separate skeletal muscle. If circuit A is activated by the brain, the motor neurons excited will contract the extensor muscle for joint 1 and the flexor muscle for joint 2, while motor neurons for the antagonistic muscles of each joint will be inhibited. Circuit A will, therefore, produce extension of joint 1

Figure 10.1
A schematic diagram of the hierarchical organization of the motor control system. The brain directs movements by selecting among spinal cord circuits, which consist of interneurons that control various combinations of motor neurons. In this example, four pools of motor neurons control the flexor and extensor muscles of two limb joints. Circuit A (in pink) produces extension of joint 1 combined with flexion of joint 2, while circuit B (in gray) produces the opposite movement. The arrows in circuits A and B indicate synaptic connections, the plus signs indicate excitatory synapses, and the minus signs indicate inhibitory synapses. The motor neurons always produce excitation of the muscles they control.



combined with flexion of joint 2. Circuit B, on the other hand, will have the opposite effect, producing flexion of joint 1 and extension of joint 2.

In addition, each of the inputs from a circuit to a given pool of motor neurons may possess unique timing, so that the activation and inhibition of different sets of motor neurons occur at different times. Imagine, for instance, that circuits A and B in Figure 10.1 were activated in alternation. If joints 1 and 2 are located in limbs on opposite sides of the body, then alternating activation of circuits A and B would produce repetitive stepping motions in the two limbs. First one limb would be flexed while the other is extended, then the opposite motion would occur. Circuits A and B might thus be part of larger circuits that produce the alternating limb movements required for locomotion (discussed in more detail later in the chapter). The main point here is that *complex sets of motor neuron activity can be selected by higher motor centers without having to specify the detailed pattern of activation. The details are inherent in the intraspinal connections of the spinal cord circuits.*

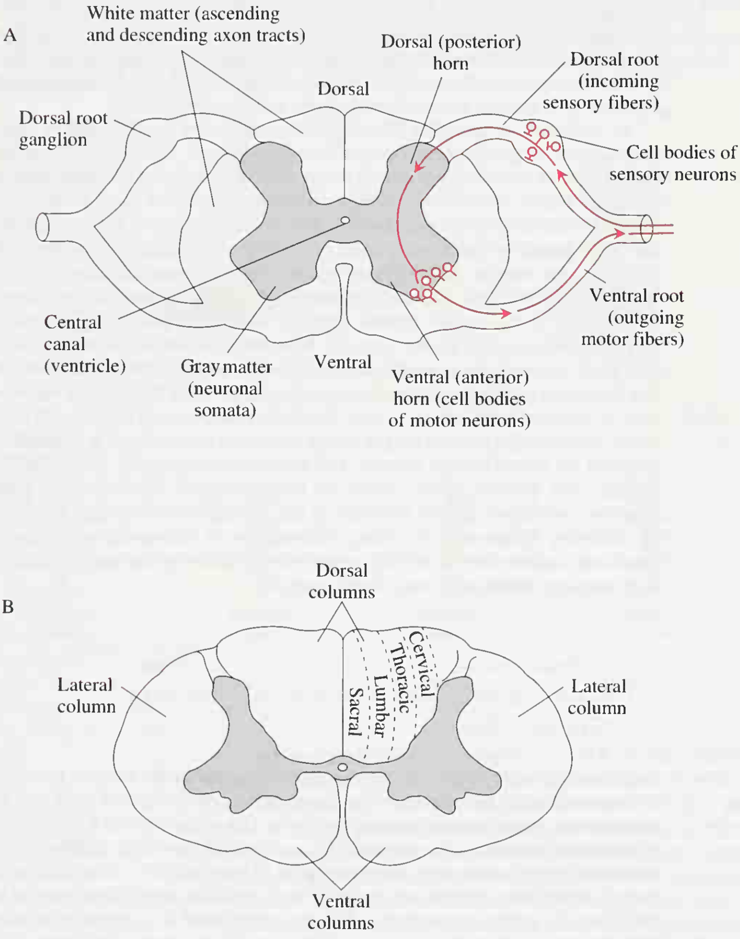
Spinal circuits are also organized so as to compensate automatically for the mechanical properties of the particular muscle groups and joints that are targeted by the circuits. Thus, the temporal order of activation of motor neuron pools will be fine-tuned in different circuits depending on the muscle mass, size of the bones, rotation angle of the joint, and other factors. In a hierarchical system, these details of organization need not be specified by higher motor centers when desired motor actions are selected.

In addition to reducing the required complexity of descending commands from higher motor centers, the spinal cord motor circuits allow automation of commonly required motor activities, without the intervention of higher motor centers. For example, the maintenance of body posture is a fundamental function of the skeletal muscle control system for any animal, and such fundamental aspects need not occupy the command resources of higher motor centers. Although the spinal motor systems can carry out the "automated" functions without intervention from higher centers, the correct functioning of the spinal circuits requires more than just the selection of prepatterned groups of motor neurons, however. The mechanisms that maintain body posture, for example, must take into account information about the deviation of joint position and muscle length from the desired values—that is, sensory information is also required. Independent of postural concerns, maintaining muscle length under changing muscle load is commonly required for many muscle actions, and this task also requires sensory information. The patellar reflex, which we have discussed extensively in prior chapters, provides a simple example of the central role of sensory feedback in initiating spinal reflexes. Thus, automation of commonly used motor functions requires the underlying neural circuits in the spinal cord to include both sensory information and motor output.

ANATOMICAL ORGANIZATION OF THE SPINAL CORD

Before we consider some specific examples of spinal reflex circuits involved in motor control, let us review the organization of the spinal cord and its sensory and motor connections to the body. The spinal cord is a long chain of repeated segments, one segment for each spinal vertebra, similar to the segmental ganglia that form the nerve cord of invertebrates. (One difference is that invertebrate ganglia are typically well separated from other ganglia in the chain by nerve connectives, while the spinal cord is a continuous cable of both nerve cell bodies and connecting axons.) As shown in Figure 10.2, nerve fibers and neuronal cell bodies are spatially segregated in the spinal cord. The cell bodies are concentrated in the more central regions of the spinal cord, while the outer layers predominantly consist of connecting

Figure 10.2
The anatomical organization of the spinal cord. The diagrams show transverse views of the mammalian spinal cord at a lower spinal level (A; lumbar spinal cord) and at a higher spinal level (B; cervical spinal cord).


A
White matter (ascending and descending axon tracts)
Dorsal (posterior) horn
Dorsal
Dorsal root (incoming sensory fibers)
Dorsal root ganglion
Cell bodies of sensory neurons
Central canal (ventricle)
Gray matter (neuronal somata)
Ventral
Ventral (anterior) horn (cell bodies of motor neurons)
Ventral root (outgoing motor fibers)
B
Dorsal columns
Lateral column
Cervical
Thoracic
Lumbar
Sacral
Lateral column
Ventral columns

axons of sensory neurons and interneurons. Because of the large amount of insulating myelin sheaths in the areas where axons dominate, these areas are more opaque than the areas where cell bodies dominate, giving the axon-containing regions a whiter appearance. Thus, the fiber tracts are known as **white matter**, while the central neuron-containing region is called **gray matter.**

The incoming sensory fibers enter the spinal cord via the dorsal roots, and the outgoing motor neuron axons exit via the ventral roots. The dorsal and ventral roots merge within the vertebral column just outside the spinal cord to form the mixed motor and sensory spinal nerve exiting each vertebral segment. After they enter the spinal cord, the sensory fibers branch out (see Fig. 1.3B), sending connections to interneurons and motor neurons in the same spinal segment and branches up and down through the white matter to make connections with neurons in adjoining spinal segments. Axon branches from the sensory neurons also extend into the brain where they deliver sensory information to the higher sensory processing centers involved in the conscious perception of body sensations, including touch, pressure, temperature, limb position, and pain (discussed in detail in Part 4 of this book).

Because the white matter consists of longitudinal fiber tracts ascending and descending along the spinal cord, the white matter is also called spinal **columns.** The butterfly-shaped gray matter divides the white matter in each half of the spinal cord into three regions: the **dorsal column**, the **lateral column**, and the **ventral column** (see Fig. 10.2). As we will discuss in chapter 11, these columns can be further subdivided into various ascending and descending tracts based on their points of origin in the brain (in the case of descending motor fibers) or their projection targets in the brain (in the case of ascending sensory fibers).

The spinal columns pick up progressively larger numbers of sensory fibers from the sensory neurons at each successive spinal segment as we move from the lower spinal cord up toward the brain. Moving from the top of the spinal cord to the bottom, the spinal columns contain fewer descending motor fibers, as the axons targeted for each successive spinal segment leave the white matter and terminate on the neurons in the gray matter at that segmental level. As a result, the proportion of the cross-sectional area of the spinal cord accounted for by the white matter becomes progressively less at lower levels of the spinal cord. For instance, the overall pattern of white and gray matter shown in Figure 10.2A would be typical of a section through the human spinal cord in the lower lumbar region. In the cervical region, however, the amount of white matter is relatively greater (see Fig. 10.2B).

The sensory axons that are added to the ascending columns at each segmental level of the spinal cord are not distributed randomly within the preexisting sensory fibers. Instead, the branches of the sensory neurons that ascend to the brain at each segment become added to the lateral part of the dorsal columns at that segment. At the higher levels of the cord, the ascending sensory fibers from the sacral spinal cord occupy the most medial part of the dorsal columns, with the lumbar and thoracic sensory axons located at intermediate positions and the cervical sensory axons found at the most lateral position.

The amount of gray matter also varies along the length of the spinal cord. In the parts of the spinal cord that innervate the forelimbs and the hindlimbs, extra motor and sensory neurons are needed to supply the muscle and skin of the limbs, as well as the more medial portions of the body. In the middle part of the spinal cord (at thoracic levels), only the neurons required to innervate the trunk are present. Thus, the gray matter in the cervical and lumbosacral parts of the spinal cord is larger than in the thoracic cord.

REFLEXES CONTROLLING MUSCLE LENGTH AND TENSION

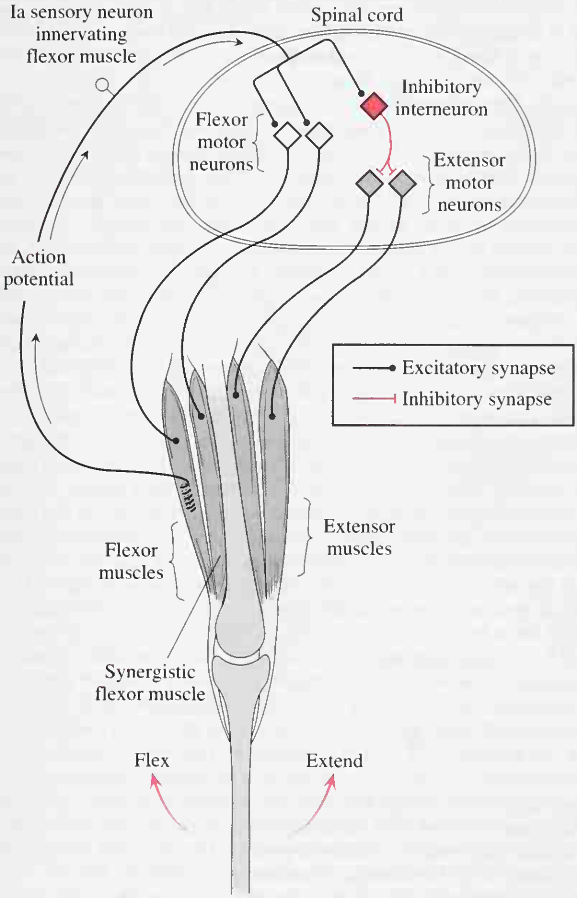
Myotatic reflex

Within the spinal cord, sensory information has local effects on spinal motor reflex circuits. The stretch reflex is a particularly simple example of the coupling between sensory and motor systems in the spinal cord. The circuitry of a stretch reflex is summarized in Figure 10.3. Passive stretch of the muscle is signaled by the sensory neurons, which make excitatory connections onto motor neurons that activate the same muscle and onto interneurons that subsequently make inhibitory connections with the motor neurons of the antagonist muscles of the same joint. In addition, the stretch-activated sensory neurons make direct excitatory connections onto motor neurons that control the synergistic (agonist) muscles of the same joint. Functionally, this combination of connections tends to maintain a constant muscle length—and thus a fixed joint position—by stimulating the muscles that restore the joint position, while relaxing the muscles that oppose the desired movement. This type of reflex, which is found in almost all skeletal muscles, is called the **myotatic reflex.** The patellar reflex is one specific example of a myotatic reflex.

The sensory neurons that carry the stretch signal into the central nervous system have the largest-diameter axons found in the spinal nerve and thus have the highest conduction velocities. The sensory axons within peripheral nerves are classified according to conduction speed, with the fastest group being called group I. The stretch-activated sensory axons, which are among the fastest of this group, are called **Ia neurons.** The motor neurons that receive direct excitatory connections from the Ia sensory neurons are the largest motor neurons, called **α motor neurons.** Because the axons of the α motor neurons are large and conduct rapidly, the signals to and from the muscle in the stretch reflex take a minimum amount of time to travel up to the spinal cord and return to the muscle. As a result of the organization of the spinal cord circuitry and the size of the neurons involved, the muscle length is tightly controlled both rapidly and automatically.

How is the "desired length" for the muscle regulated? In most joints, the joint possesses a wide range of possible motions and positions, depending on the task in which the animal is engaged and the organism's posture. Each position of the joint corresponds to different lengths of the muscles that

Figure 10.3
The neuronal circuitry of the myotatic reflex. This diagram of the stretch reflex illustrates the circuitry for a *flexor* reflex (the patellar reflex is an *extensor* reflex). It reminds us that stretch reflexes are a general mechanism and are not restricted to extensor reflexes. The excitatory neurons are drawn in black and the inhibitory neurons appear in red. The extensor motor neurons are shaded gray.



govern it. Thus, a mechanism must be available to reset the stretch sensors so that they can detect change of length over the complete range possible for the muscle. To understand how this mechanism works, we begin by examining the structure of the sensory receptors within the muscle itself.

Muscle spindles: the sensory receptors for muscle stretch

In our schematic diagrams of the circuitry underlying the stretch reflex (see, for example, Fig. 10.3), we have always portrayed the sensory ending in the muscle as a spiral wrapped around muscle fibers like a spring. The actual endings of Ia sensory fibers in the muscle really do form such spirals around individual muscle fibers, and a more anatomically correct illustration of this arrangement is shown in Figure 10.4.

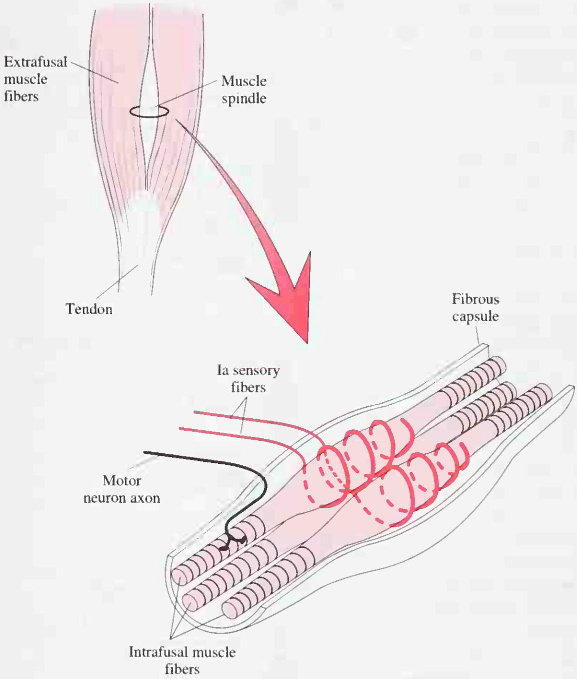
The muscle fibers wrapped by the sensory endings are not identical to those that constitute the bulk of the skeletal muscle and provide the power for moving loads. Instead, a specialized subset of muscle fibers (called **intrafusal muscle fibers**) receives the sensory endings. The intrafusal fibers are separated both functionally and anatomically from the other muscle fibers (called **extrafusal muscle fibers**) that make up the muscle. Scattered throughout skeletal muscles, in parallel with the extrafusal muscle fibers, are specialized structures called **muscle spindles** because of their spindle shape (fat in the middle, thin at the ends) when viewed through a light microscope. Figure 10.4 shows that inside the fibrous capsule that surrounds each muscle spindle there are several intrafusal muscle fibers, which are similar to extrafusal muscle fibers except that the central portion of each fiber lacks the contractile machinery. The Ia sensory fibers form their spiral endings (called **annulospiral endings**) around the muscle fibers in this central region.

The intrafusal muscle fibers also receive inputs from axons of motor neurons, as do extrafusal fibers. However, because the intrafusal muscle fibers are few in number and short in length, activation of their motor neurons produces no detectable contraction of the muscle. We will discuss the functional importance of the motor inputs to the intrafusal muscle fibers shortly.

The mechanical behavior of intrafusal muscle fibers and the resulting response of the sensory neuron are illustrated schematically in Figure 10.5. The extrafusal muscle fibers parallel the intrafusal fibers. When the length of the intrafusal fibers is matched to the resting length of the muscle as a whole (see Fig. 10.5A), action potentials are discharged from the sensory neuron slowly. If a weight is attached to the muscle, generating a passive stretch of both the extrafusal and intrafusal fibers, the annulospiral ending of the sensory neurons will detect the stretch of the central portion of the intrafusal fibers, and the frequency of action potentials in the sensory neurons will increase dramatically. The activation of the sensory neuron arises because the sensory endings contain stretch-sensitive ion channels that open upon mechanical deformation, producing a depolarization of the sensory ending and stimulating action potentials. (Mechanosensitive ion channels will be discussed in more detail in the description of sensory systems in Part 4.)

Figure 10.5B shows what happens to the sensory response of the muscle spindle when the motor neurons supplying the extrafusal muscle fibers are stimulated to fire action potentials. The muscle undergoes an active

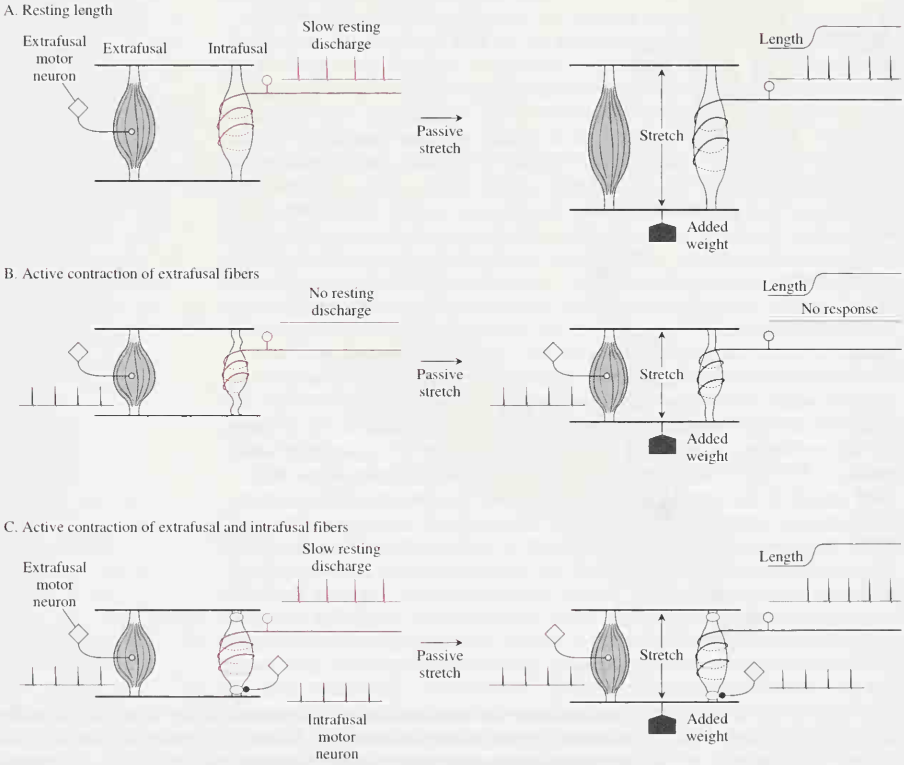
Figure 10.4
The anatomical organization of the muscle spindle stretch receptor. Encapsulated structures (muscle spindles) parallel the muscle fibers making up the bulk of the muscle (extrafusal muscle fibers). As shown in the magnified view in the lower part of the figure, the capsule of the spindle contains specialized muscle fibers (intrafusal muscle fibers) that receive sensory fibers (shown in red) from group Ia sensory neurons. The sensory fibers spiral around the muscle fibers. The intrafusal muscle fibers also receive inputs from motor neurons.



contraction, but the intrafusal muscle fibers remain the same length, relieving the resting stretch of the intrafusal fibers. The resting discharge of the sensory neurons therefore halts during the muscle's contraction. If a passive stretch is then produced by increasing the weight on the contracted muscle, the length of the intrafusal fibers will increase. Because the starting length is no longer matched to the length of the muscle as a whole, however, the increase in muscle length may prove insufficient to stimulate action

Figure 10.5

The response of a muscle-spindle sensory neuron to stretch of the muscle under various conditions. Extrafusal and intrafusal muscle fibers are arranged in parallel. (A) When passive stretch is applied to a resting muscle in which the length of the intrafusal muscle fibers matches the resting length of the extrafusal fibers, the rate of action potentials in the sensory neuron increases. (B) During active contraction of the extrafusal muscle fibers, the muscle shortens and the load on the intrafusal muscle fibers is removed. The firing of action potentials in the sensory neuron stops, and the sensory neuron fails to respond to a passive stretch of the muscle. (C) The resting discharge and the sensitivity to stretch of the sensory neuron are restored if the intrafusal muscle fibers are stimulated to contract along with the extrafusal muscle fibers during contraction of the muscle.



potentials in the sensory neurons. Thus, during active contraction, the sensitivity of the stretch sensors becomes disrupted and the nervous system has no way to regulate muscle length.

Motor innervation of intrafusal muscle fibers

The intrafusal muscle fibers also possess a contractile apparatus and are innervated by motor neurons, which can stimulate their active contraction. The effect of stimulating the intrafusal motor neurons, together with the extrafusal motor neurons, is illustrated in Figure 10.5C. In this case, the intrafusal muscle fibers contract, maintaining the resting level of stretch of the central mechanosensory region. Under these conditions, the slow resting discharge of the sensory neurons is retained during the active contraction. Compare this effect with the absence of resting activity noted during active contraction if no stimulation of the intrafusal motor neurons occurs (see Fig. 10.5B). When the intrafusal motor neurons are stimulated, a passive stretch of the muscle can be detected, because the length of the intrafusal fibers is adjusted to accommodate the new, reduced length of the muscle during active contraction (see Fig. 10.5C). The active response of the intrafusal muscle fibers stimulated by the intrafusal motor neurons is key to maintaining the ability of the stretch sensor system to respond to changes in muscle length across the entire range of length of which the muscle is capable.

The motor neurons that supply the intrafusal muscle fibers form a separate pool of motor neurons within the population that controls a particular muscle. This permits higher motor centers of the nervous system, as well as spinal cord circuits, to activate separately the extrafusal and the intrafusal motor neuron pools supplying a muscle. In mammals, the intrafusal pool can be distinguished from the extrafusal pool on the basis of axon diameter and hence conduction velocity of the action potentials. Whereas the extrafusal fibers are supplied by the large-diameter fibers of the α motor neurons, the intrafusal fibers of mammals are supplied by the slower-conducting, smaller fibers of the **γ motor neurons.**

The intrafusal pool of motor neurons can be further subdivided according to the properties of the intrafusal muscle fibers they activate. Muscle fibers within the muscle spindle fall into one of two functional classes: static fibers and dynamic fibers. **Static fibers** and the sensory fibers that innervate them provide the sustained action potentials that give a steady indication of muscle length. **Dynamic fibers** and their sensory fibers are most sensitive to the rapid changes in length that accompany the onset of a muscle stretch.

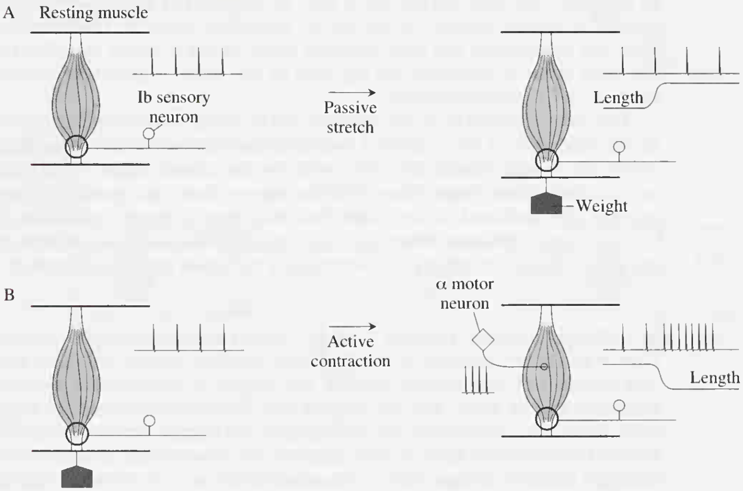
Tendon reflex

In addition to muscle spindles, skeletal muscles are supplied with another type of specialized sensory receptors. These receptors, which are called **tendon organs** or **Golgi tendon organs**, are located at the junction between extrafusal muscle fibers and the tendon that connects the muscle to other body structures. (In contrast, muscle spindles are located within the muscle fibers of the muscle.) Each tendon organ is an encapsulated structure containing a mesh of collagen fibers connected to the ends of the muscle fibers.

The sensory fiber entering the tendon organ gives rise to many branches that intertwine among the mesh of collagen fibers. The sensory neurons of the tendon organ include large axons that are members of the fast-conducting group I, like the sensory neurons of muscle spindles. Because the sensory neurons of tendon organs conduct action potentials a bit more slowly than the muscle spindle receptors, however, they are called group Ib sensory neurons to distinguish them from the faster-conducting group Ia fibers.

The behavior of the tendon-organ sensory neuron during passive stretch differs significantly from that of the muscle-spindle sensory neuron. Figure 10.6A shows how the tendon-organ receptor responds during passive stretch. At the resting muscle length, there is a slow resting discharge of action potentials at a rate that depends on the resting tension in the muscle. When the muscle is passively stretched, the firing rate of the tendon-organ receptor changes very little. In contrast, the muscle-spindle sensory neuron (see Fig. 10.5A) fires briskly when the muscle is passively stretched from the resting length.

Figure 10.6
The response of the Golgi tendon-organ sensory neuron during passive stretch and active contraction of the muscle. The Golgi tendon organ is arranged in series with the extrafusal muscle fibers. (Contrast this arrangement with that of the muscle spindle, shown in Figure 10.5.) (A) During passive stretch of the muscle, the increase in length is absorbed by the muscle fibers but not by the tendon. The rate of action potentials in the group Ib sensory neurons remains unaffected by the passive stretch. (B) During active contraction, the force generated by the muscle is transmitted to the joint via the tendon, which deforms the Golgi tendon organ and increases the rate of action potentials in the sensory neuron.



During active contraction, the two types of sensory receptors also respond quite differently. Figure 10.6B shows the response of the tendon-organ receptor during active contraction. In this case, when the muscle contracts and exerts tension on the tendon, the rate of action potentials in the sensory neuron of the tendon organ increases. In contrast, muscle-spindle sensory neuron either ceases firing during active contraction (in the absence of coactivation of the intrafusal motor neuron; see Fig. 10.5B) or maintains its resting firing rate (during coactivation of the intrafusal motor neuron; see Fig. 10.5C).

What accounts for these important differences in the sensitivity of tendon-organ sensory neurons and muscle-spindle sensory neurons to passive and active stretch of the muscle? The answer lies in the mechanical properties of the muscle fibers versus those of the tendon and in the relationship between the sensory structure and the extrafusal muscle fibers in the two cases. The tendon and muscle fibers of the muscle are arranged *in series*. When a weight is applied to passively stretch the muscle/tendon combination, most of the stretching is confined to the muscle fibers, and the length of the tendon changes very little. This situation arises because the tendon is relatively stiff, unlike the unstimulated muscle fibers. The longitudinally oriented contractile filaments of the muscle cells (see chapter 9) can slide past one another readily to facilitate the increase in length during the stretch. Because the intrafusal muscle fibers of the muscle spindles are aligned *in parallel* with the other muscle fibers, they will become elongated during the passive stretch, activating the group Ia afferent fibers that signal the stretch to the nervous system. On the other hand, the collagen mesh within the Golgi tendon organ will not be significantly distorted during the passive stretch, and the intertwined branches of the sensory fiber will not be activated.

During an active contraction, the mechanical situation is quite different. In this case, the muscle fibers themselves *generate* the force applied to the muscle. Because the muscle fibers transfer their force to the attached body structures via the tendons, the contracting muscle fibers pull the collagen mesh within the Golgi tendon organ. This action distorts the mesh, squeezing the intertwined branches of the innervating group Ib sensory fibers and increasing the rate at which action potentials are generated in the sensory neuron. The degree of tendon-organ distortion that arises during the active contraction depends on the amount of force applied to the tendon by the contracting muscle. If the muscle tension is high, as in lifting a heavy weight, the tendon organ becomes highly distorted, and the sensory neuron of the tendon organ will fire action potentials at a rapid rate. If the muscle tension is low during the contraction, however, the collagen mesh within the tendon organ will not be distorted very much, and the sensory neuron will fire action potentials at a lower rate.

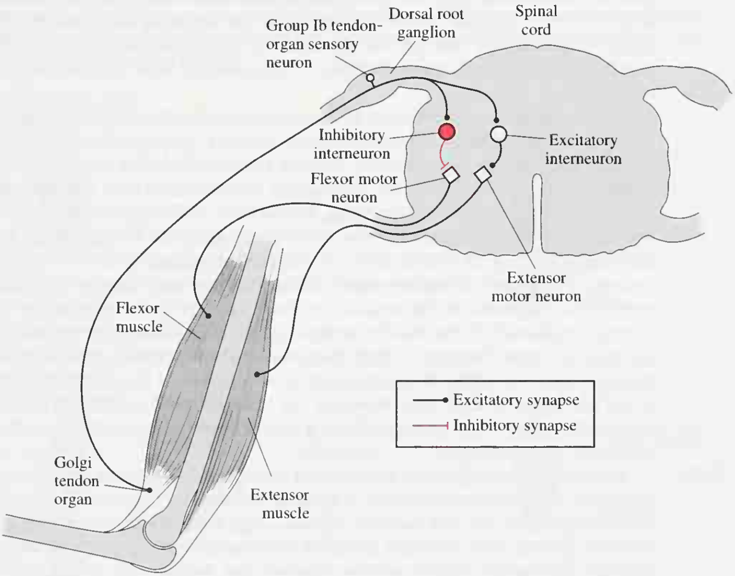
Because of their different mechanical arrangements relative to the muscle fibers of a muscle, the group Ia sensory neurons of the muscle spindles and the group Ib sensory neurons of the Golgi tendon organs provide the nervous system with different kinds of information about the state of the muscle. *The muscle spindle sensory neurons give information about* ***muscle***

length,* *while the tendon-organ sensory neurons give information about* *muscle tension.

Let us consider how this different sensory information is utilized in spinal-cord reflex circuits. As we saw earlier, the muscle-spindle sensory information is used in stretch reflexes (like the patellar reflex) in ways that make sense for the automatic regulation of muscle length by spinal motor control systems. We will now focus on how the reflex circuits in the spinal cord use information provided by Golgi tendon organs.

Figure 10.7 provides a schematic diagram of a typical tendon reflex circuit. Like the other sensory neurons of spinal nerves, the cell bodies of the Golgi tendon-organ sensory neurons are located in the dorsal root ganglion, just outside the spinal cord. For the sake of simplicity, the figure includes only the connections made from the tendon organ of a single flexor muscle; in reality, every muscle controlling a joint possesses its own complement of tendon organs. The group Ib afferent fiber branches after it enters the spinal

Figure 10.7
The neuronal circuitry underlying the tendon reflex, or inverse myotatic reflex. The sensory neuron makes excitatory synapses on interneurons. The interneurons then make inhibitory synapses on the motor neurons controlling the same muscle and excitatory synapses onto motor neurons controlling the antagonist muscles of the joint. The inhibitory neuron is shown in red.



cord, forming excitatory synaptic connections on both inhibitory and excitatory interneurons. The inhibitory interneuron (shown in red in Figure 10.7) makes inhibitory synaptic connections onto the pool of motor neurons controlling the same muscle from which the tendon-organ sensory fiber originated (in Figure 10.7, they are flexor motor neurons). When the tension in the muscle rises, the sensory neuron of the tendon organ fires action potentials at a more rapid rate, which increases the excitation of the inhibitory interneurons. The resultant increased firing of the interneurons inhibits the flexor motor neurons. Because the flexor motor neurons are inhibited, the flexor muscle will contract less strongly and the tension in the muscle will decrease. This process represents an example of a **negative feedback loop.**

This feedback loop, which is based on muscle tension, allows the nervous system to set and maintain a desired muscle tension, just as the muscle spindle reflex system—together with the intrafusal motor neurons—enables the nervous system to set and maintain a desired muscle length. The inhibitory interneurons receive both inhibitory and excitatory connections from other spinal interneurons and from descending axons coming from higher motor control centers in the brain. These connections create a mechanism by which the nervous system can set the desired muscle tension.

In our discussion of neuronal integration in chapter 8, we saw that the various inhibitory and excitatory inputs to a neuron sum in time and space to determine whether the neuron fires an action potential. Thus, if a large amount of muscle tension is desired for a particular muscle, the inhibitory interneurons in the tendon reflex for that muscle can be inhibited by other intraspinal inputs. In this case, a large amount of excitation from the group Ib sensory fibers from the muscle, corresponding to a large muscle tension, will be required to overcome the inhibition of the inhibitory interneurons and release the inhibitory feedback. Conversely, if a small muscle tension is required, then the inhibitory interneurons of the tendon reflex can be excited by the other neural circuits. In this case, a relatively small amount of excitation from the group Ib fibers, corresponding to a low muscle tension, will be sufficient to cause the inhibitory feedback to be manifested.

In addition, the group Ib afferent fiber from the Golgi tendon organ makes excitatory synapses on a separate group of excitatory interneurons, which in turn make excitatory synaptic connections on the motor neurons controlling the antagonist motor neurons of the same joint (the extensor motor neurons in our example). The effect of the tendon reflex (inhibition of the same muscle, excitation of the antagonist) is the opposite of that associated with the stretch reflex (excitation of the same muscle, inhibition of the antagonist). For this reason, the tendon reflex is also called the **inverse myotatic reflex** (recall that the stretch reflex is also called the myotatic reflex).

The stretch reflex involves a direct connection from the sensory neuron onto the motor neurons; in the tendon reflex, the sensory neurons connect with only interneurons, which then form the appropriate connections with motor neurons. Because only a single level of synaptic connection is present in the stretch reflex circuit in the spinal cord (the excitatory synapse between the sensory neurons and the motor neurons), the stretch reflex is called a **monosynaptic reflex.** The tendon reflex, on the other hand, is a **polysynaptic reflex** in which the signal from the sensory neurons must pass through more than one synaptic relay before reaching the motor neurons. Monosynaptic reflexes occur with the greatest speed, because they include the minimum number of relay steps (one) before the signal returns to the muscle. In contrast, polysynaptic reflexes give the nervous system more opportunities to modify and alter the behavior of the reflex circuitry by permitting integration of multiple signals within the pools of interneurons.

Self-inhibition of motor neurons: Renshaw cells

In chapter 9, we saw that the nervous system can avoid fatigue of the muscle fibers within a motor unit by firing bursts of action potentials in a motor neuron, separated by quiet periods between bursts (see Fig. 9.17). By staggering the bursts in different pools of motor neurons, smooth and steady increases in muscle tension can be attained without fatiguing the muscle as a whole and without significant jitters in tension. A simple spinal-cord feedback circuit, involving a type of inhibitory interneuron called the **Renshaw cell,** helps to produce the desired oscillations in the firing rate of motor neurons. Before the axon of a motor neuron exits the spinal cord via the ventral root, it gives off a collateral branch that remains within the spinal cord and makes excitatory synaptic connections with local inhibitory interneurons, the Renshaw cells. As shown in the diagram in Figure 10.8, the Renshaw cells then make an inhibitory synaptic connection back onto the same motor neuron. This kind of self-inhibitory synaptic connection is called **recurrent inhibition.**

The behavior of this system is summarized in Figure 10.8B. If a motor neuron is stimulated by strong excitatory input from some neural source, it will fire action potentials at a high rate. This firing triggers summated contraction of the muscle fibers making up the motor unit controlled by the motor neuron (as described in chapter 9). In addition, the action potentials in the motor neuron produce strong excitation of the Renshaw cell via the excitatory synapses made by the collateral branch of the motor neuron's axon. Strong inhibition of the motor neuron results, produced by the feedback inhibitory synapses of the Renshaw cell. This recurrent inhibition causes the firing rate of the motor neuron to decline, which in turn translates into weaker excitation of the Renshaw cell and thus into weaker recurrent inhibition. If the excitatory input from other sources persists, the motor neuron will fire again at a faster pace, producing a new burst of action potentials at a rapid rate. The motor neuron then returns to the beginning of the cycle shown in Figure 10.8B. Thus, the motor neuron will tend to oscillate between periods of high firing rate and periods of low firing rate.

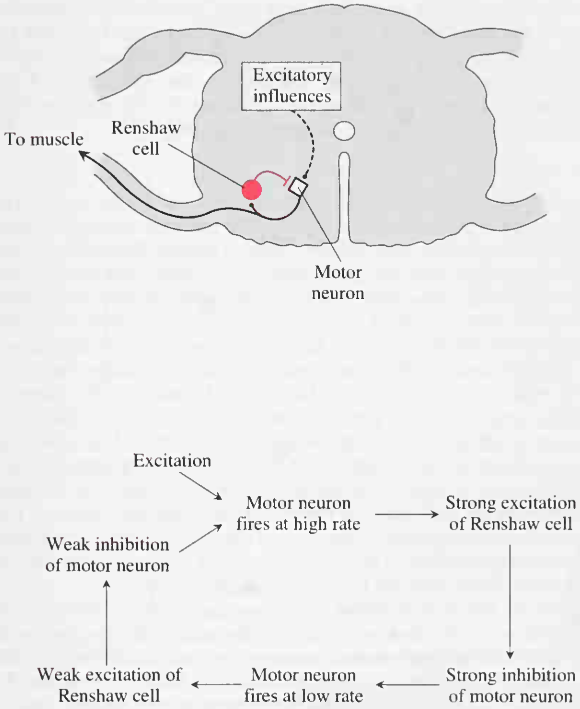

Excitatory influences
Renshaw cell
To muscle
Motor neuron
Excitation
Motor neuron fires at high rate
Strong excitation of Renshaw cell
Weak inhibition of motor neuron
Strong inhibition of motor neuron
Motor neuron fires at low rate
Weak excitation of Renshaw cell

Figure 10.8
Renshaw cells produce self-inhibition of motor neurons. The axons of motor neurons send branches that make excitatory synapses onto the Renshaw cells (shown in red). The Renshaw cells in turn make inhibitory synapses back onto the same motor neurons. The cyclical behavior of this circuit is summarized in the lower diagram.

The Withdrawal Reflex: An Example of a More Complex Reflex Circuit

At one time or another, everyone has had the unpleasant experience of eliciting another type of spinal reflex, the limb withdrawal reflex. If you accidentally touch a hot object, your hand will be rapidly jerked away from the object—without your body issuing the command and indeed before the perception of pain reaches a conscious level. Similarly, if you step on a piece of glass hidden in the sand while walking barefoot on the beach, your leg will rapidly flex to withdraw the foot—again without conscious control. In concert with the flexion of the injured leg, the other leg will extend, to take the weight of the body and keep you from falling over (during a normal gait, your other leg would have been flexed at the time when the injured leg was extended, placing the foot in contact with the glass). A variety of other reflexive rearrangements of upper limb and trunk musculature would also occur to shift the body weight off the injured leg and onto the other leg without your body toppling over. Thus, limb withdrawal reflexes triggered by noxious stimuli are characterized by two actions: the withdrawal of the stimulated limb and the extension of the contralateral limb together with postural rearrangements to maintain support of the body.

Withdrawal of the stimulated limb

Let us consider first the withdrawal component of the reflex circuit (Fig. 10.9). If the hand encounters a hot object, pain-sensitive sensory neurons will be stimulated. Like the other sensory neurons already discussed, the cell bodies of these sensory neurons are located in the dorsal root ganglia, just outside the spinal cord. The axons of the pain-sensitive sensory cells branch within the spinal cord and make excitatory synaptic connections with various types of spinal interneurons. In Figure 10.9, two types receive inputs from the sensory neuron. Both interneuron types then make excitatory connections with the next neurons in the circuit. In one case, the target of the excitatory connection is a pool of interneurons that excite the flexor motor neurons of the limb receiving the painful stimulus. In the other case, the targets are inhibitory interneurons that make inhibitory synaptic connections with the motor neurons controlling the extensor muscles of the limb receiving the stimulus. Activation of the sensory neurons then activates two parallel circuits, culminating in contraction of the flexor muscles and relaxation of the extensor muscles. This process produces the rapid, involuntary withdrawal of the limb from the hot, pain-inducing object.

For simplicity, Figure 10.9 shows only the muscles of a single joint. In reality, the pain-sensitive sensory neurons make similar connections with all of the flexor and extensor motor neurons controlling all joints in the limb (for example, finger, wrist, elbow, and shoulder joints in the case of a human arm). The connections with the motor neurons are indirect, involving a polysynaptic pathway through at least two layers of intervening interneurons.

Extension of the contralateral limb

In our initial description of withdrawal reflexes, we noted that flexion of the stimulated limb is combined with extension of the contralateral limb to maintain support of the body. This extension requires additional neuronal circuitry in the spinal cord to activate and inhibit the appropriate motor neurons controlling the contralateral limb. This is shown in Figure 10.10. Because the motor neurons controlling the contralateral limb lie on the side of the spinal cord away from the entry point of the sensory information, the

Figure 10.9
The neuronal circuitry underlying limb withdrawal in response to a painful stimulus. The sensory neuron makes excitatory synapses onto pools of excitatory interneurons in the spinal cord. These interneurons then excite other interneurons, which in turn excite the flexor motor neurons of the injured limb and inhibit the extensor motor neurons.

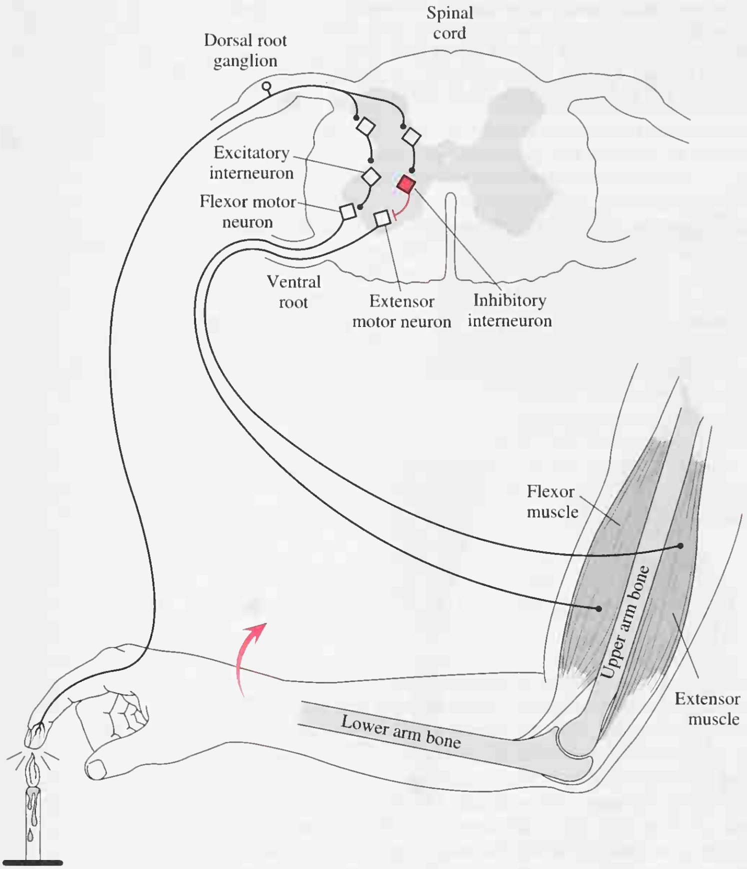
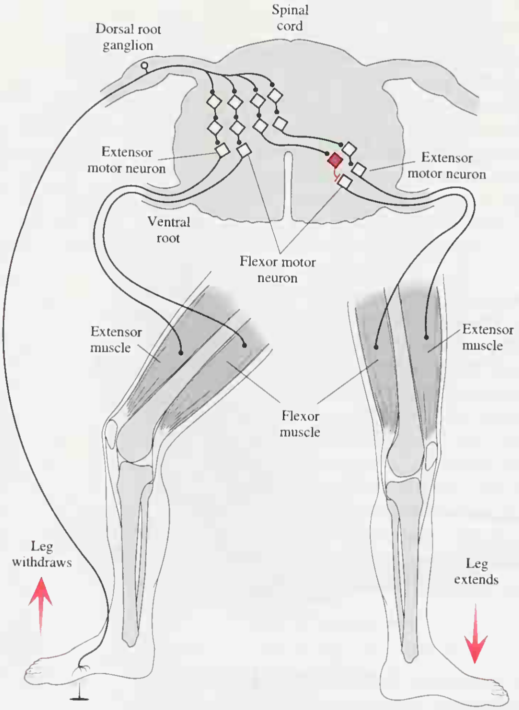


Figure 10.10
The expanded circuitry for the withdrawal reflex, combining flexion of the injured limb with extension of the contralateral limb. The ipsilateral portion of the circuit is the same as in Figure 10.9, producing excitation of the flexor motor neurons and inhibition of the extensor motor neurons for the ipsilateral limb. The sensory neurons stimulate two additional pools of interneurons, which make excitatory synapses onto excitatory interneurons that cross to the other side of the spinal cord and connect with pools of interneurons controlling the motor neurons of the contralateral limb. These interneurons produce the opposite effect on the contralateral limb, exciting the extensor motor neurons and inhibiting the flexor motor neurons.



sensory neurons must stimulate interneurons that cross the midline of the spinal cord and terminate on the opposite side. The pain-sensitive sensory neurons make excitatory synaptic connections with a group of interneurons, which then activate another pool of interneurons that send axons to the contralateral spinal cord. There, the interneurons make excitatory synapses with the pools of inhibitory and excitatory interneurons that control the flexor and extensor motor neurons for the contralateral limb. In this case, however, the activated pools of interneurons are the opposite of those described for the ipsilateral part of the spinal cord (see Fig. 10.9). That is, the inhibitory interneurons of the flexor motor neurons are activated while the excitatory interneurons of the extensor motor neurons are activated. This leads to contraction of the muscles that extend the limb, while the opposing flexor muscles relax. In this way, the flexion of the stimulated limb is accompanied by extension of the contralateral limb.

The circuitry of the withdrawal reflex is actually more complicated than illustrated in Figure 10.10, which shows only a single segment of the spinal cord. The intermediate interneurons send connections to both higher and lower spinal cord segments, contacting appropriate pools of interneurons on both sides of the spinal cord to maintain stable body posture during the withdrawal of the injured limb. These connections in complex reflex circuits are clearly much more elaborate than the simple myotatic reflexes that control the length of a single skeletal muscle. Indeed, because the withdrawal reflex involves the coordinated activity of many pools of motor neurons, it serves as a transition between purely reflexive circuits (which are activated by a particular sensory stimulus) and more general spinal circuits (which underlie voluntary, coordinated activity of the organism). As an example of the second type, we will consider the spinal circuits involved in locomotion.

SPINAL CIRCUITS CONTROLLING LOCOMOTION

To this point, we have discussed several types of spinal reflex circuits, ranging from the simple monosynaptic reflex arc of the stretch reflex to the complex polysynaptic circuits involved in the withdrawal reflex. One principle emerges from a consideration of these circuits: pools of spinal neurons controlling a particular function are used as parts of various neuronal circuits.

A trivial example of this principle involves the motor neurons themselves. Because they represent the only way that the nervous system can actually control the contraction of the skeletal muscles, the motor neurons that innervate a particular muscle must be part of any neural circuit that involves that muscle.

Other, less obvious examples also exist. Consider the pools of inhibitory and excitatory spinal interneurons that make synaptic connections on the group of motor neurons controlling an extensor muscle of a limb. These interneurons may be parts of various reflex circuits. In the stretch reflex, for instance, the inhibitory pool of interneurons for the extensor-muscle motor neurons will be excited by the group Ia sensory neurons from the flexor muscle (see Fig. 10.3). In addition, the extensor-muscle inhibitory interneurons will be excited during the activation of the withdrawal reflex for a limb (see Fig. 10.9). The excitatory interneurons for the same extensor muscle will participate in still other reflex circuits. For example, the excitatory interneurons for a particular extensor muscle will be excited by stimulating the Golgi tendon organ of the antagonist flexor muscle (see Fig. 10.7) and by stimulating the withdrawal reflex for the contralateral limb (see Fig. 10.10). This flexibility is one of the advantages of a hierarchical arrangement of motor control, as we discussed earlier in this chapter (see Fig. 10.1).

Groups of interneurons like those used in spinal reflex circuits can also be utilized in other kinds of spinal motor circuits to control the organism's movement through space—the process of **locomotion.** We have already seen that the circuitry of the withdrawal reflex can produce flexion of a limb in combination with extension of the contralateral limb. For the contralateral limb, mirror-image withdrawal circuitry produces the reverse effect. If the nervous system can alternately excite the two populations of interneurons—one on each side of the spinal cord—that are used in the limb withdrawal circuits for the two limbs, then it can produce alternating limb movements of the type used in quadruped locomotion. Of course, locomotion includes much more than just alternating stepping motions of the limbs, but the basic pattern can be produced by circuitry of the type shown in Figure 10.10.

In both mammals and other vertebrates, the spinal cord contains not only the circuits required for the basic alternating stepping pattern, but also the circuits that produce interlimb coordination under changing conditions and varying speeds of locomotion. When the spinal cord is transected at a high level to eliminate all descending commands from the brain, proper patterns of limb movements like those seen during voluntary locomotion can still be elicited. Even after elimination of the sensory inputs from the limbs, the alternating stepping movements of locomotion can still be observed in animals with spinal cord transections. Thus, the basic pattern of motor output during locomotion is produced by **central pattern generators** that do not require sensory information from the limbs to generate the correct motor pattern. Nevertheless, sensory input about joint position, muscle tension, and other factors is normally present during walking and is used to adapt the motor pattern to the changing conditions that are encountered as the animal moves. Without sensory information, the central pattern generators can still generate the alternating cycles of flexion/extension, but the resulting movements are stereotyped and easily disrupted. In other words, both automatic generators of motor patterns and sensory information are required to produce normal locomotion.

The spinal circuits underlying central pattern generators

The central pattern generators and the interlimb coordination circuits that produce locomotion are probably made up of spinal interneurons that include some of the same interneuron pools governing simpler spinal reflexes. The spinal circuits corresponding to the central pattern generators that control the alternating excitation of the interneurons in the appropriate spinal segments and the circuits producing the appropriate intersegmental coordination are not yet understood in detail in quadruped vertebrates. In less complex vertebrates such as fish, however, the body movements required for locomotion (that is, swimming) are somewhat simpler, and the underlying spinal circuits are easier to understand. In addition, at least some of the basic features of the motor scheme evolved in animals that swim are likely retained in the spinal organization of their terrestrial descendants.

For the purposes of illustrating spinal locomotion mechanisms, we will therefore describe the neural circuits that control swimming in fish. In keeping with the principle of hierarchical organization, the brain does not have to program the alternating activation of motor neurons on the two sides of the body to produce swimming. Instead, it issues a generalized activation command to the spinal cord, and spinal cord circuits at each body segment and the intersegmental connections among these circuits produce the correct sequence of muscle contractions. The brain says "swim," and the spinal cord obliges.

What motion is required to produce effective swimming? Although the details depend on the exact situation (for example, body position, water currents, and other conditions), a basic pattern can be discerned, as illustrated in Figure 10.11A for a prototypical fish. A wave of contraction propagates from the head to the tail along each side of the body, with the waves on each side occurring out of phase with one another. This action produces an undulating motion that propels the animal through the water. Many fish also possess a variety of fins that contribute to propulsion through the water, as well as to steering and body orientation during locomotion. In our example, however, we will simplify the situation by considering only the generation of the propagating wave of contraction. Comparing the positions of the body undergoing contraction at times 1 and 3 in Figure 10.11A, we see that the swimming movement is produced by the alternating contraction of the muscles on the two sides of the body at each body segment.

Let us first examine the circuit that produces these alternating contractions in each body segment, using the lamprey as a model. The basic circuit that generates swimming in the lamprey, a primitive jawless fish, is shown schematically in Figure 10.11B. Swimming is initiated by action potentials in motor command axons descending along both sides of the spinal cord from brain command centers located bilaterally in the brainstem. These motor command axons make excitatory synaptic connections with the pattern generator neurons on both sides of the spinal cord at each spinal segment (each is enclosed by a dashed box in Figure 10.11B). Although the diagram shows only a single spinal segment for simplicity, the pattern is actually repeated at each level along the spinal cord. The command neurons provide a steady level of excitation that adds to the inputs arising from the connections among the pattern generator neurons themselves and from other spinal sources (for example, sensory inputs). The pattern of action potentials in the command axons does not in itself provide information about the alternating rhythm of output from the motor neurons on the two sides of the spinal

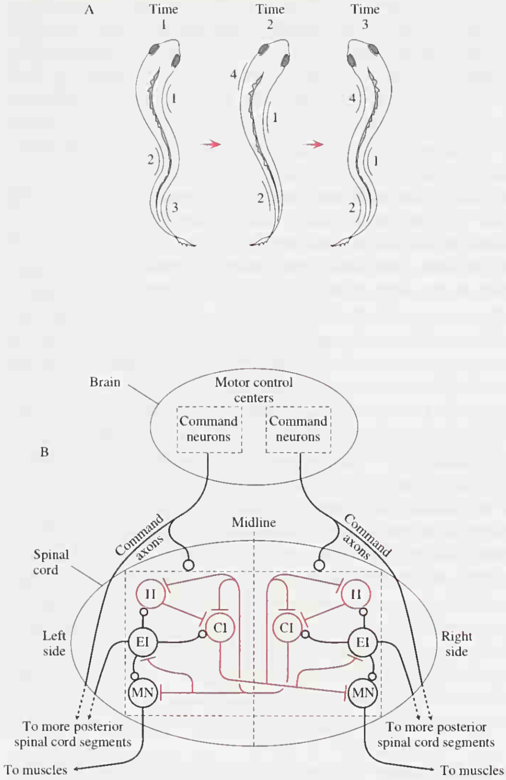


Figure 10.11
The neuronal circuitry that produces alternating contractions on the two sides of the body when the lamprey swims. Although the circuitry for a single spinal cord segment is shown, the same pattern of connections is repeated along the entire spinal cord. (A) A schematic diagram of the undulating motion during swimming in the lamprey. At time 1, the right-side muscles are contracting, which produces bending to the right, at positions 1 and 3; in the middle of the animal, the contraction appears on the left side, at position 2. At a later time (time 2), the contraction of the right side has moved to a more posterior position (position 1), as has the contraction on the left side (position 2). A new wave of contraction on the left side has just begun (position 4). Still later (time 3), the waves of contraction on the two sides of the body have moved to still more posterior positions. (B) A circuit diagram for the central pattern generator of swimming at a single spinal cord segment. The circuits on the two sides of the spinal cord (enclosed in dashed boxes) are mirror images of one another. The network is activated by descending excitatory inputs that arise from swimming command centers in the brain. Inhibitory neurons are indicated in red.

cord. On the other hand, the rate of action potentials in the command axons does influence the overall level of excitability in the pattern generators and thus the period of oscillation.

How does the circuit in Figure 10.11B produce alternating excitation to the muscles on both sides of the body? The swimming command axons make excitatory connections onto four types of neuron on each side of the spinal cord: the motor neurons themselves, and three kinds of interneuron. A crossed interneuron (CI in the figure) sends an axon to the opposite side of the spinal cord, where it makes inhibitory synapses onto all four types of neuron in the contralateral circuit. An excitatory interneuron (EI) makes excitatory synapses onto the other three types of the neuron on the same side of the spinal cord, and an inhibitory interneuron (II) makes inhibitory synapses onto the crossed interneurons on the same side of the spinal cord.

During swimming, action potentials are triggered in the command axons on both sides. As a result, both parts of the bilateral pattern generator circuit receive steady excitation. Because of other excitatory influences (such as sensory inputs) and modulatory inputs onto the brainstem command centers, one side of the circuit will reach the threshold to initiate a burst of action potentials before the other. For example, if the right-side neurons fire first, the combination of the direct excitatory input from the command axons and the excitatory input from the excitatory interneuron will cause the motor neurons on the right to fire, contracting the muscles on that side and causing the body to bend to the right. This would correspond to time 1, position 1, in Figure 10.11A, for example. In addition, the summed excitation from the command axons and the excitatory interneuron activates the crossed interneuron. Action potentials in this interneuron tend to suppress activity in the contralateral neurons, prompting the contralateral muscles to relax. This situation will continue for some time, with a burst of action potentials in the right-side motor neurons accompanied by a corresponding silent period in the left-side motor neurons.

To produce alternating bursts of action potentials in the motor neurons of the two sides, the burst on the right side must be terminated. Nothing in the synaptic circuitry of the network shown in Figure 10.11B would appear capable of halting the activation of the motor neurons once the process has begun. Burst termination occurs principally because of the membrane electrical properties of the motor neurons and the excitatory interneurons themselves. The action potentials of these neurons exhibit pronounced after hyperpolarizations caused by calcium-activated potassium channels (see chapter 5). As calcium accumulates inside the neurons, these after hyperpolarizations summate during the series of action potentials, causing the frequency of action potentials to decline and finally eliminating them altogether. Thus, the motor neurons and excitatory interneurons fire action potentials in discrete bursts, separated by quiet periods, even in the presence of sustained excitatory input from the command axons.

This example clearly indicates the importance of cellular mechanisms in determining the behavior of neural networks. *In general, a diagram of the connections between neurons is not sufficient to predict the behavior of the circuit.* Additional information about the ion channels and electrical characteristics of the individual neurons making up the circuit is essential to understand nervous system function.

As the burst of activity on the right side proceeds, the activation of the crossed interneuron falls off because of the declining excitation provided by the excitatory interneurons and the delayed inhibition arising from the inhibitory interneuron, which is excited by the command axons and the excitatory interneuron. Thus, coincident with the declining burst activity on the right side, the inhibition of the contralateral network decreases. This decline allows the continuing excitation supplied to the contralateral network by the descending command axons to reach the threshold for activation of the network on the left side of the spinal cord. As soon as the burst of action potentials in the left network begins, activation of the crossed interneuron from that side produces inhibition of the right network and ensures termination of the right-side burst. At this stage, the state of the network is a mirror image of the starting condition, with excitation of the left-side motor neurons and inhibition of the right-side motor neurons. The resulting body position is also the mirror image (see, for example, time 3, position 4, in Figure 10.11A).

Intersegmental control of central pattern generators

Effective locomotion requires not only alternating contraction on both sides of the body at each segment, but also anterior-to-posterior propagation of the contraction along each side (see Fig. 10.11A). To produce this pattern, the central pattern generator networks at more posterior positions must be activated progressively later than the networks at more anterior positions. The axons from the brainstem motor command centers descend the entire length of the spinal cord and deliver excitation to all of the segmental pattern generators. Not all of these generators are equally excitable, however, and the segmental network with the highest excitability will be the first to be activated. The level of excitability of a segmental network might be regulated by other influences, such as the activity of additional excitatory or inhibitory interneurons, which generate e.p.s.p.'s or i.p.s.p.'s that sum with the e.p.s.p.'s produced by the command axons. Under ordinary conditions, the most excitable pattern generators will be those at the rostral (anterior) end of the spinal cord. Thus, alternating contraction of the body musculature will begin at the anterior end.

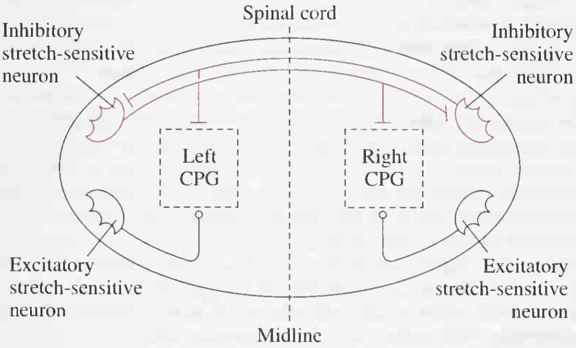
In addition to the excitatory connections described above, the excitatory interneuron of each segmental oscillator network also sends an axon branch that forms excitatory synapses onto the neurons of the ipsilateral networks in neighboring spinal cord segments (see the dashed line in Figure 10.11B). The excitation descending from the anterior pattern generator sums with the excitation from the command axons to bring the more posterior segmental pattern generator to the threshold level and initiates alternating activity in the network. The activity of the excitatory interneuron in this segment is then transmitted to the next most posterior segment, initiating activity in the pattern generator network at that location. In this manner, activity of the pattern generators sweeps down the spinal cord, producing the propagating wave of contraction. Similarly, when the activity in the first-activated network (that is, at the anterior end) switches over to the contralateral side, the excitatory interneuron on that side will excite the more posterior ipsilateral network, and a contraction wave will sweep down that side of the body. In this way, the segmental pattern generators of the spinal cord program the oscillating contractions of each part of the body, while the intersegmental excitatory connections couple the oscillators in the proper sequence to produce effective swimming.

Sensory inputs modulate the central pattern generators

The central pattern generator circuitry can produce swimming motions in the absence of any sensory input about muscle length or body posture. This fact leads to an important principle: *rhythmic behaviors can be generated by the central nervous system, without requiring sensory information to produce the* *pattern.* This does not mean that sensory inputs have no effect on the rhythmic behavior, however. In the lamprey swimming circuit, for example, sensory neurons sensitive to the stretching of the body act to reinforce and adjust the timing of the alternating bursts of action potentials within the swimming circuits on the two sides of the spinal cord. In Figure 10.11A, note that when the right side of the body is contracting at a particular position, the left side is being stretched (see, for example, time 1, position 1). Stretch-sensitive sensory neurons are stimulated to fire action potentials whenever the body is stretched in this manner.

We discussed stretch-sensitive sensory neurons earlier in this chapter, in our description of the reflexes controlling muscle length and tension in mammals. In the lamprey, however, the stretch-sensitive neurons are actually located within the spinal cord itself and are stimulated by the bending of the spinal cord during the undulations, rather than by stretching of the muscles of the body wall. The stretch-sensitive neurons and their synaptic connections are diagrammed in Figure 10.12. To make the wiring diagram less confusing, the circuitry shown in Figure 10.11B is lumped together on each side of the spinal cord and labeled CPG (for central pattern generator). The stretch-sensitive neurons are found along the lateral edges of the spinal cord (and are called edge cells for that reason) and have dendrites that spread laterally along the margin of the cord. When the muscles on the right side contract and bend the body toward the right, the left side of the spinal cord becomes stretched and the edge cells on that side will fire action potentials.

Figure 10.12
The effects of stretch-sensitive sensory neurons on the swimming pattern generator in the spinal cord of the lamprey. The stretch-sensitive neurons are located within the spinal cord, at the lateral edges. The dashed boxes represent the bilateral central pattern generator networks shown in Figure 10.11. The inhibitory sensory neurons and their synaptic connections are shown in red.


Spinal cord
Inhibitory stretch-sensitive neuron
Inhibitory stretch-sensitive neuron
Left CPG
Right CPG
Excitatory stretch-sensitive neuron
Excitatory stretch-sensitive neuron
Midline

Two types of edge cells are found on each side of the spinal cord: excitatory and inhibitory. The excitatory cells make excitatory synaptic connections onto the neurons forming the CPG circuit on the same side of the spinal cord. The inhibitory cells make inhibitory connections onto the neurons of the CPG on the contralateral side of the spinal cord, including the inhibitory edge cells on the other side. When the right-side CPG is active and the body bends to the right, the left-side stretch-sensitive cells become activated. Excitation is then added to the left-side CPG, just as the burst of activity in the right-side CPG begins to wane. The additional excitation, combined with the decreasing inhibition crossing from the contralateral CPG, will ensure that the burst of activity begins in the left-side CPG, producing the next phase of the alternating cycle of activity on the two sides of the spinal cord. Similarly, when the body bends to the right, the left-side inhibitory edge cell fires action potentials. This inhibits the right-side CPG, helping to end the burst of activity on the right side. Thus, the stretch-sensitive sensory neurons help coordinate the network, ensuring that the bursts of activity in the two parts of each segmental swimming circuit alternate properly.

In the generation of rhythmic behavior, the basic pattern is produced by the way neurons in the central nervous system are wired together and by the cellular properties of the neurons in the network. Sensory information serves to reinforce the pattern and ensure that activity in the circuit is tailored to the environment in which the movement occurs.

SUMMARY

Hierarchical organization of motor control systems allows higher centers to control complex movements without having to specify the details of the activity of individual motor neurons. The spinal cord contains circuits that automate commonly needed motor functions. The stretch reflex (or myotatic reflex) is a simple example of such an automated function, which allows the nervous system to maintain a fixed length of a muscle automatically.

In the stretch reflex, sensory information about muscle length comes from specialized muscle fibers called intrafusal muscle fibers, which are contained within an encapsulated sensory structure known as the muscle spindle. The annulospiral endings of group Ia sensory neurons are stimulated to fire action potentials when the length of the muscle spindle increases as a result of passive stretch of the muscle. The intrafusal muscle fibers are innervated by motor neurons, which can stimulate active contraction of the intrafusal muscle fibers and allow the muscle spindle to signal passive stretch over a wide range of resting muscle length.

The Golgi tendon organ is another muscle sensory receptor that gives the nervous system information about the tension of a muscle. This information, which is transmitted to the spinal cord by group Ib sensory neurons, is used in the tendon reflex (also called the inverse myotatic reflex).

Pools of excitatory and inhibitory interneurons that make synaptic connections onto motor neurons are activated by sensory neurons as part of the reflex circuits controlling muscle length and tension. In addition, motor neurons make self-inhibitory synaptic connections via a class of inhibitory interneurons called Renshaw cells. The withdrawal reflex is an example of a more complex reflex circuit involving interneurons on both sides of the spinal cord. In this reflex, flexion of the stimulated limb is combined with extension of the contralateral limb and with postural adjustments.

Interneuron circuits similar to those found in the withdrawal reflex are also likely involved in non-reflex spinal cord networks such as those controlling movements during locomotion. The basic patterns of movements are produced by central pattern generators located in the spinal cord. For example, alternating contractions on both sides of the body underlie basic locomotor behavior such as swimming. These contractions are produced by spinal cord interneuron networks that depend on both synaptic connections and intrinsic electrical properties of the neurons to produce alternating activation of the motor neurons on the two sides of the spinal cord. Through excitatory coupling among the segmental pattern generators, contractions are propagated along the body as required for effective swimming. Although the basic pattern is produced by intrinsic properties of the central network, sensory input from stretch receptors helps to reinforce and coordinate this pattern.

11

Brain Motor Mechanisms

In chapter 10, we discussed some of the spinal cord circuits that regulate and coordinate movement. These circuits can generate both simple behavior, such as stretch and tendon reflexes, and complex coordinated activities, such as locomotion. As an animal moves around and interacts with its environment, however, these low-level control circuits are normally combined in ever-changing ways to produce appropriate actions. These less stereotypical, goal-directed actions are the responsibility of motor control systems found in higher parts of the brain. In this chapter, we will present an overview of the higher motor systems and their functional interconnections.

MOTOR CONTROL CENTERS ARE FOUND IN THE BRAINSTEM, MIDBRAIN, AND FOREBRAIN

One of the evolutionary trends discussed in chapter 2 is the trend toward increasing cephalization. The brainstem, which is the most phylogenetically primitive part of the brain, contains many of the brain circuits that regulate spinal cord motor mechanisms and modulate motor activity based on sensory information. In simple vertebrates like the lamprey, the brainstem circuits perform virtually all of the integrative motor functions responsible for guiding the animal's motor behavior. During the course of brain evolution, the forebrain increased in size and complexity, but the brainstem motor mechanisms were retained, providing an intermediate level of control in the motor hierarchy. Thus, the brainstem contains regions that act independently to control spinal motor systems, but in addition the brainstem is used by forebrain motor centers as a go-between in guiding motor behavior.

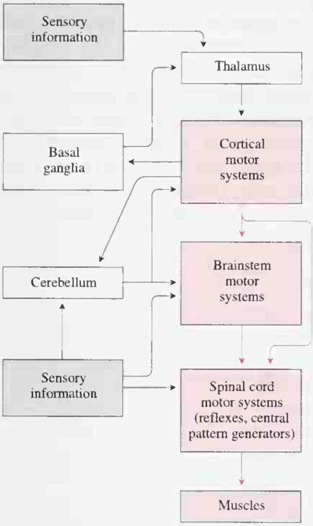
In mammalian brains, the trend toward increasing importance of the forebrain is manifested principally in the evolution of proportionally larger amounts of the brain devoted to the cerebral cortex. In addition to the forebrain-to-brainstem route of descending motor control (called the **corticobulbar system**), the evolution of larger cortical areas is accompanied by development of a second, direct route of descending motor control (called the **corticospinal system**). This route bypasses the brainstem areas and projects directly to the lower levels of the hierarchy in the spinal cord. In general, the larger the cortex, the greater the influence of the corticospinal system on motor behavior. Although exceptions exist, the brainstem motor systems tend to govern more global motions, such as swimming in fish or alternating swinging of limbs during walking in tetrapods. In contrast, the corticospinal system provides for finer motor control, such as the motions your fingers make on a computer keyboard as you type.

Figure 11.1 shows a block diagram of some connections among the motor system components in a mammalian nervous system. The core of the system consists of the central axis of cortical, brainstem, and spinal cord motor systems (shown in red in the diagram). At the spinal cord level, the system provides the basic circuitry for controlling the muscles, including the reflexes and central pattern generators discussed in chapter 10. The spinal cord in turn receives commands from both the brainstem and the motor cortex. In addition to the connections to the spinal cord, the cortex sends descending axons that terminate in the brainstem motor centers. This central axis receives inputs from other brain regions involved in motor coordination—most notably the **cerebellum**, which is part of the hindbrain, and the **basal ganglia**, which span the border between the forebrain and midbrain. Each of these modulatory motor systems will be discussed later in this chapter.

Motor output must be altered based on sensory information. For example, during locomotion, the orientation of the body in space changes continually, and the movements of body parts must be updated to take this into account. Thus, sensory information (shaded gray in Figure 11.1) provides input to the motor control systems at every level of the hierarchy. In the spinal cord, information about muscle length and muscle tension is employed in spinal reflexes, and information about body bending or limb position influences the activity of central pattern generators (see chapter 10). Sensory information also helps to determine the outputs from brain motor centers. The cerebellum, for instance, monitors ongoing activity in the core motor control systems and reinforces or suppresses that activity, based on sensory information. Maintenance of balance and proper body posture during locomotion is one example of motor modulation involving the cerebellum.

Figure 11.1

A block diagram of the flow of information in the hierarchy of motor systems. The arrows indicate the direction of connections, but do not imply monosynaptic connections. In all cases, information transfer at the cellular level involves a combination of excitatory and inhibitory synaptic influences. The term "sensory information" is used generically—that is, sensory information about the body or the environment enters the network at several levels, and the different types of sensory information are not distributed equally among all parts of the network.



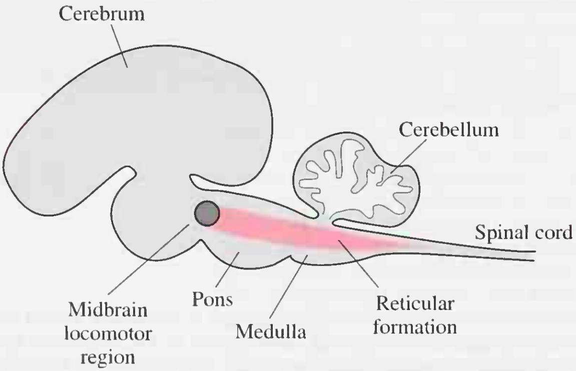
BRAINSTEM MOTOR AREAS

In the lamprey, swimming is initiated in response to excitatory inputs descending in the spinal cord from command centers in the brainstem (see chapter 10). Similar motor command centers for locomotion are found in higher vertebrates. Electrodes can be placed into brainstem nuclei to deliver brief electrical stimuli that activate action potentials in nearby neurons and axons, thereby mimicking the effect of natural activation of this part of the brain. If trains of electrical stimuli are applied in this way to certain regions in the midbrain of a mammal, coordinated locomotion can be induced and the animal can be made to walk on a treadmill. It is worth emphasizing again that the pattern of the electrical stimuli carries no inherent information about the pattern of the stepping motion. Instead, the stimulation in the brainstem serves only as a trigger for spinal cord networks that produce the appropriate motions. If the brainstem stimulation is strengthened by increasing either the electrical current or the rate at which stimuli are administered, the speed of locomotion increases accordingly. In other words, an animal can be induced to walk, trot, or gallop, depending on the strength of electrical stimulation applied to the brainstem initiator regions.

Reticulospinal system

The brainstem locomotor region lies at the upper end of the midbrain, near the anterior extreme of a diffuse network of neurons called the **reticular formation** (red shaded area in Figure 11.2). The reticular formation (*reticulum* means "net" or "mesh") runs along the lower part of the brainstem from the midbrain into the medulla; it contains neurons having a variety of sensory and motor functions, including the regulation of arousal. Among these reticular neurons are cells that send axons down into the spinal cord, forming the **reticulospinal tract.** These axons make synaptic connections onto interneurons and motor neurons involved in spinal reflexes. In the lamprey,

Figure 11.2
The location of the midbrain locomotor region in the mammalian brain. The red shaded region shows the reticular formation, which extends from the midbrain into the medulla.



reticulospinal neurons carry the motor commands for initiation of swimming. In mammals, similar neural systems originating in the reticular formation are also likely important in relaying locomotor commands.

The neurons of the reticular formation receive sensory information from several sources, including the sensory projections ascending into the brain from the spinal cord. The sensory information carried by these ascending neurons—regarding limb position, muscle length, muscle tension, and so on—is used to modify the motor commands descending in the reticulospinal axons, providing the sensory feedback necessary to alter the strength of motor excitation as required by the locomotor state of the animal.

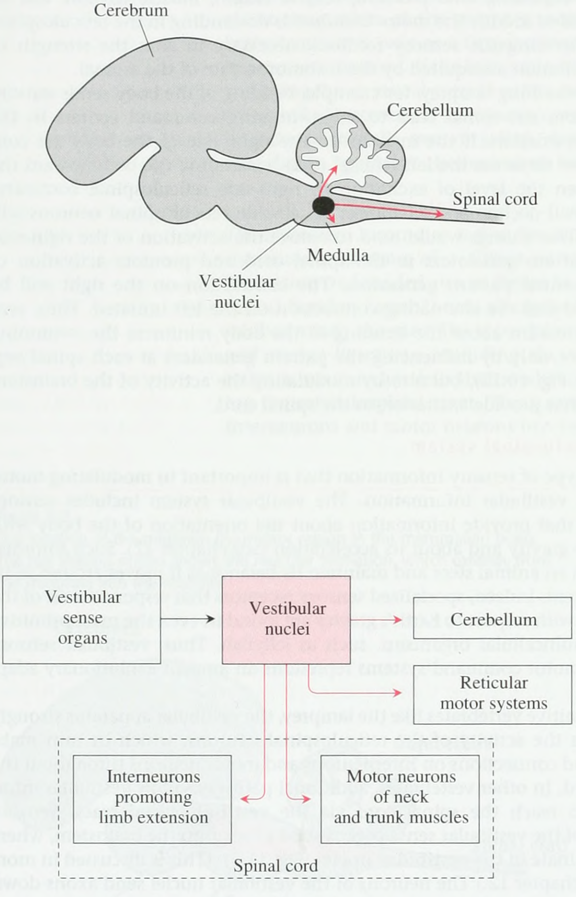
In a swimming lamprey, for example, bending of the body sends sensory signals from the spinal cord to the swimming command centers in the reticular formation. If the muscles on the right side of the body are contracted and those on the left relaxed (that is, bending the body toward the right), then the level of excitation in right-side reticulospinal command neurons will decline and excitation in left-side reticulospinal neurons will increase. This change would tend to reduce the activation of the right-side central pattern generators in the spinal cord and promote activation of left-side central pattern generators. The contraction on the right will be terminated and the alternating contraction on the left initiated. Thus, sensory information about the bending of the body reinforces the swimming pattern not only by influencing the pattern generators at each spinal segment (see Fig. 10.12), but also by modulating the activity of the brainstem neurons that provide excitation to the spinal cord.

Vestibulospinal system

Another type of sensory information that is important in modulating motor output is vestibular information. The vestibular system includes sensory receptors that provide information about the orientation of the body with respect to gravity and about its acceleration (see chapter 12). Such information helps an animal steer and maintain its balance as it moves around in its environment. Indeed, specialized sensory receptors that respond to tilt of the organism with respect to Earth's gravity are found in even the most primitive mobile multicellular organisms, such as jellyfish. Thus, vestibular sensory input to motor command systems represents an ancient evolutionary adaptation.

In primitive vertebrates like the lamprey, the vestibular apparatus strongly influences the activity of the reticulospinal neurons, which in turn make widespread connections on interneurons and motor neurons throughout the spinal cord. In other vertebrates, additional pathways allow vestibular information to reach the spinal cord via the **vestibulospinal tract**. Sensory neurons of the vestibular sense organs send axons into the brainstem, where they terminate in the **vestibular nuclei** (Fig. 11.3). (This is discussed in more detail in chapter 12.) The neurons of the vestibular nuclei send axons down into the spinal cord, where they make two different types of synaptic connections (see Fig. 11.3). First, excitatory synapses are made onto pools of interneurons controlling the motor neurons of limb muscles. These pools consist of the excitatory interneurons of the extensor motor neurons and the

Figure 11.3
The location of the vestibular nuclei in the brainstem. The block diagram summarizes some of the connections made by the neurons (red) of the vestibular nuclei. In addition to the spinal cord, the vestibular nuclei send axons to the cerebellum and to the reticular motor systems.



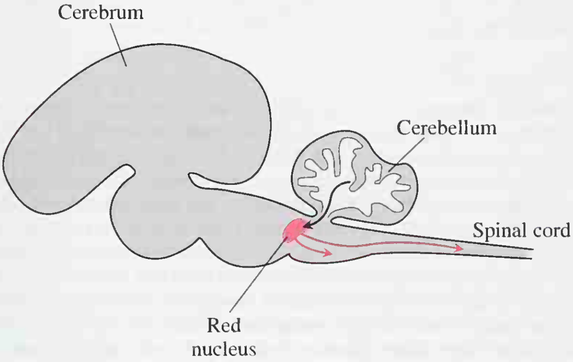
inhibitory interneurons of the flexor motor neurons. Thus, action potentials descending from the vestibular nuclei polysynaptically excite extensor motor neurons and inhibit flexor motor neurons, promoting extension of all four limbs. Second, axons from neurons in the vestibular nuclei make direct excitatory and inhibitory synaptic connections onto motor neurons that control the muscles of the neck and the trunk of the body. These connections make reflexive adjustments of head and body position in response to tilt and rotation, both of which commonly occur during locomotion.

The vestibular nuclei also send axons to the cerebellum (see Fig. 11.3), which aids in the maintenance of balance and body posture (as discussed later in this chapter). The vestibular nuclei also make other connections not shown in Figure 11.3, including an important connection to the motor neurons controlling the eye muscles. (The role of this vestibular input in oculomotor reflexes will be discussed in chapter 12.) The vestibular input to the cerebellum plays a role in these oculomotor reflexes, especially in the modification of oculomotor reflexes based on experience. (The role of vestibular inputs to the cerebellum in reflex plasticity will be considered in chapter 21.)

Rubrospinal system

The **red nucleus** is another brainstem region that contributes to descending control of spinal-cord motor functions. This nucleus is located near the anterior end of the midbrain, as shown in Figure 11.4. A major source of input to the red nucleus is the cerebellum (see below). The neurons of the red nucleus send axons that descend into the spinal cord, forming the

Figure 11.4
The location of the red nucleus in the brainstem. The red nucleus receives inputs from the cerebellum (black arrow) and sends outputs to the spinal cord via the rubrospinal tract (red arrow). It also sends inputs to other brainstem regions.



rubrospinal tract. In the spinal cord, these axons form excitatory synapses on interneurons that in turn excite flexor motor neurons of the limbs. Thus, activation of the neurons in the red nucleus promotes limb flexion. Activation of the vestibulospinal tract has the opposite effect—limb extension. The balance between activity in the red nucleus and in the vestibular nuclei is important, therefore, in determining the overall equilibrium between flexor and extensor muscle systems of the limbs.

CORTICAL MOTOR AREAS

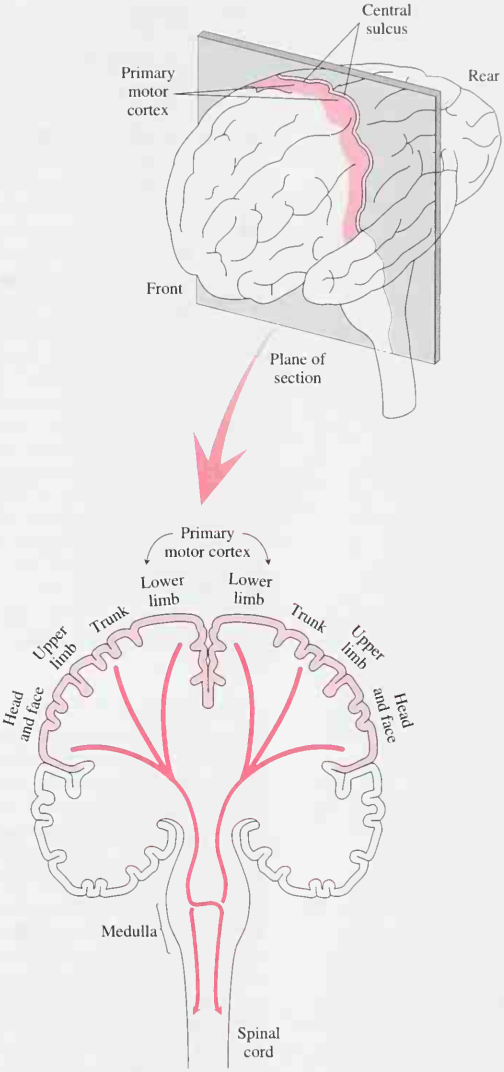
In many animals (particularly in more primitive vertebrates), the brainstem motor areas provide all the circuitry necessary to initiate and coordinate movement. As the forebrain blossomed during the course of evolution, however, other control mechanisms associated with the forebrain came on the scene. As discussed earlier in this chapter, motor regions of the cerebral cortex arose to augment and, in some cases, partly supplant the motor control function of the more primitive brainstem, especially in mammals. As shown in Figure 11.1, the descending motor commands from the cortex project directly to the spinal cord via the corticospinal tract, bypassing the brainstem and giving the cortex direct control of spinal circuits. The cortex also sends inputs to the brainstem via the corticobulbar tract, providing further indirect control of spinal circuits.

An important source of the descending cortical tracts is the **primary motor cortex**, illustrated in Figure 11.5. It is located on the **gyrus** (or outfolding of the cortex), just in front of the deep groove (or **sulcus**) that runs laterally across the surface of the brain about halfway between its front and back. This groove is called the **central sulcus.** The primary motor area is also called the **precentral cortex** to indicate that it is located on the precentral gyrus, just in front of the central sulcus. Based on microscopic differences in cellular architecture, neuroanatomists divide the human cortex into broad areas designated by numbers. The primary motor cortex corresponds to **area 4** in the commonly used numbering scheme of Brodmann.

Representation of the body in primary motor cortex

In the nineteenth century, a combination of anecdotal observations on human patients with head wounds and experimental observations on the brains of animals provided evidence that motor function is localized in the precentral gyrus. Stimulation of the primary motor cortex on the left side of the brain was found to give rise to movements on the right side of the body, while stimulation of the right precentral gyrus caused movements on the left side. This contralateral control of the body arises because the descending axons of the corticospinal tract cross (or **decussate**) from one side of the brain to the other as they pass through the medulla, just before entering the spinal cord. Thus, the axons from the right motor cortex enter the left side of the spinal cord, where they make synaptic connections onto motor neurons

Figure 11.5
The primary motor cortex, which is organized somatotopically, is a strip of cortex located on both sides of the cerebral cortex, just in front of the central sulcus (see the three-dimensional view in the upper part). The lower part shows a diagram of the organization of the cortex, as seen in cross section. Neurons located in the most medial portion, near the midline, control the muscles of the lower limbs, with successively more lateral portions controlling the trunk, upper limb, head, and face. The descending axons from the motor cortex (red arrows) cross the midline in the medulla and then descend in the contralateral spinal cord.



controlling the muscles of the left half of the body. The reverse holds true for the axons from the left motor cortex. In the medulla, the axons from motor cortex form large bundles, called the **pyramids**, and the point of crossing is called the **pyramidal decussation.**

In addition to the gross functional organization into regions controlling the left and right sides of the body, the primary motor cortex on each side of the brain is subdivided into regions that control specific parts of the body. There is an orderly progression as we move from the most medial to the most lateral portions of the motor cortex. Figure 11.5 shows the organizational scheme, which is known as the **somatotopic organization** of primary motor cortex. The most medial parts of precentral cortex control the hindlimb, and the most lateral parts control the head and mouth. The body trunk and forelimbs are controlled by the intermediate parts of motor cortex. Within the hindlimb region, an orderly progression is observed from the toes in the most medial portion, to the hip in the most lateral portion (see Fig. 11.5). Similarly, in the forelimb region, there is a progression from the medial portion to the lateral portion, but in the opposite direction. That is, the shoulder is controlled by the most medial part of the region, and the digits of the forepaw by the most lateral portion.

Although this basic somatotopic scheme is universal in the motor cortex, the amount of cortex in a specific species that is devoted to a particular muscular group reflects the relative importance of that muscle group for that species. For instance, in primates—and especially in humans—the amount of motor cortex devoted to the control of the hand and fingers is particularly large, in keeping with the great importance of the hand in primate motor behavior. Similarly, in the region devoted to the face in primate motor cortex, the majority of the neurons are involved in movements of jaw, lips, and tongue.

Microscopic anatomy of the motor cortex

The primary motor cortex (Brodmann's area 4) represents only one small part of the overall cerebral cortex. The cortex is a thin sheet of cells, a few millimeters thick, that forms the outer surface of the cerebral hemispheres, like the rind of an orange. Like other parts of the cortex, the motor cortex has a layered structure. Its layers are defined based on microscopic examination of the types of cells and their densities, as summarized in Figure 11.6. At the outermost edge of the cortex, layer I consists primarily of incoming axons that make synapses onto dendrites of neurons found in deeper layers. Layers II and III, the next deeper layers, contain large numbers of neuronal cell bodies, whose axons project predominantly to other cortical regions, either nearby or some distance away. The neurons in layers II and III have cell bodies that are shaped like pyramids, with a broad base that tapers into a long dendrite extending toward the cortical surface (see Fig. 11.6B). Consequently, this type of neuron is called a **pyramidal cell**. The apical dendrites receive numerous synaptic connections from the incoming axons running through layer I. Although the distinction between layers II and III is not readily apparent in most parts of the cortex, the cell bodies of the pyramidal neurons in layer II tend to be smaller than those in layer III.

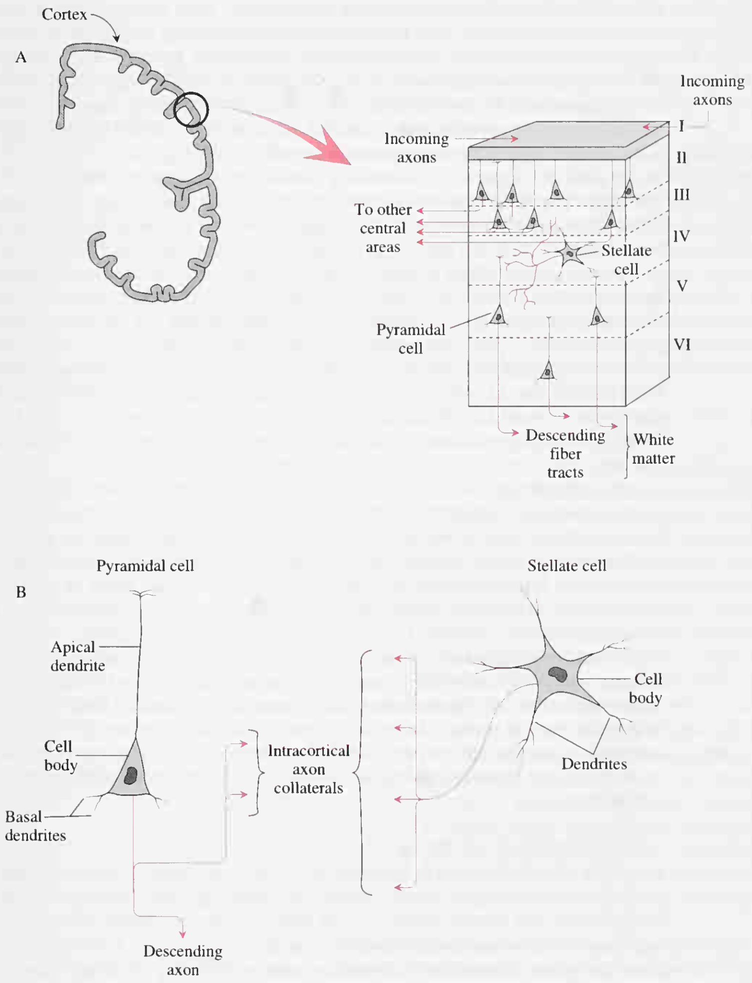


Figure 11.6
The microscopic anatomy of the cerebral cortex. (A) The cortex is organized in cellular layers, numbered with Roman numerals I–VI (right). Pyramid-shaped pyramidal cells are found in layers II, III, V, and VI. Star-shaped stellate cells are found in layer IV. (B) Schematic drawings of the structures of pyramidal cells (left) and stellate cells (right) of cerebral cortex.

Layer IV contains neurons with multiple dendrites that radiate out from a roughly spherical cell body; for this reason, these star-shaped neurons are called **stellate cells** (see Fig. 11.6B). Unlike the pyramidal cells, whose axons can project long distances to make connections with other regions of the central nervous system, the stellate cells' axons remain in the same vicinity, making synapses predominantly on nearby neurons. The stellate cells receive inputs from axons carrying sensory information into the cortex. For this reason, cortical regions that focus on sensory processing have greater numbers of stellate cells and a thicker, more pronounced layer IV. The primary motor cortex (Brodmann's area 4) is principally an output region that sends motor commands to non-cortical motor areas. Consequently, layer IV is not well developed in area 4—an anatomical aspect that prompted Brodmann to distinguish the precentral gyrus as a separate cortical region.

By contrast, layer V is particularly prominent in primary motor cortex. This layer contains pyramidal neurons whose cell bodies are the largest among the pyramidal cells. These neurons give rise to axons that descend long distances to carry motor commands to the brainstem and spinal cord. In the motor cortex, the largest of the pyramidal neurons in layer V (called **Betz cells**) give rise to the largest and fastest-conducting axons that descend through the medullary pyramids into the spinal cord. In the non-motor portions of the cortex, the pyramidal cells of layer V are a major source for outputs from the cortex to other brain regions, including the thalamus and basal ganglia (see below). The axons of these pyramidal cells commonly give rise to one or more collateral branches that remain within the cortex (see Fig. 11.6B), providing information about the outgoing activity to local cortical circuits.

Layer VI—the final cellular layer—contains neurons that send axons to other non-cortical areas of the central nervous system. An important target of descending connections from these neurons is the **thalamus.** As we will describe in more detail in chapters focusing on sensory systems, the thalamus is a complex group of nuclei that process and relay various kinds of sensory information. In addition, some areas of the thalamus receive extensive inputs from brain motor control systems, including the motor cortex, and are important in the regulation of motor output. Layer VI of the motor cortex is a major source of axons that project to the motor parts of the thalamus.

Beneath layer VI, the outgoing axons form the myelinated fiber tracts of the cerebral white matter. As with the spinal cord white matter, the whitish color arises because the densely packed myelin sheaths of the axon bundles make the tissue more opaque than the overlying layers containing neuronal cell bodies.

Encoding of movement by neurons of the primary motor cortex

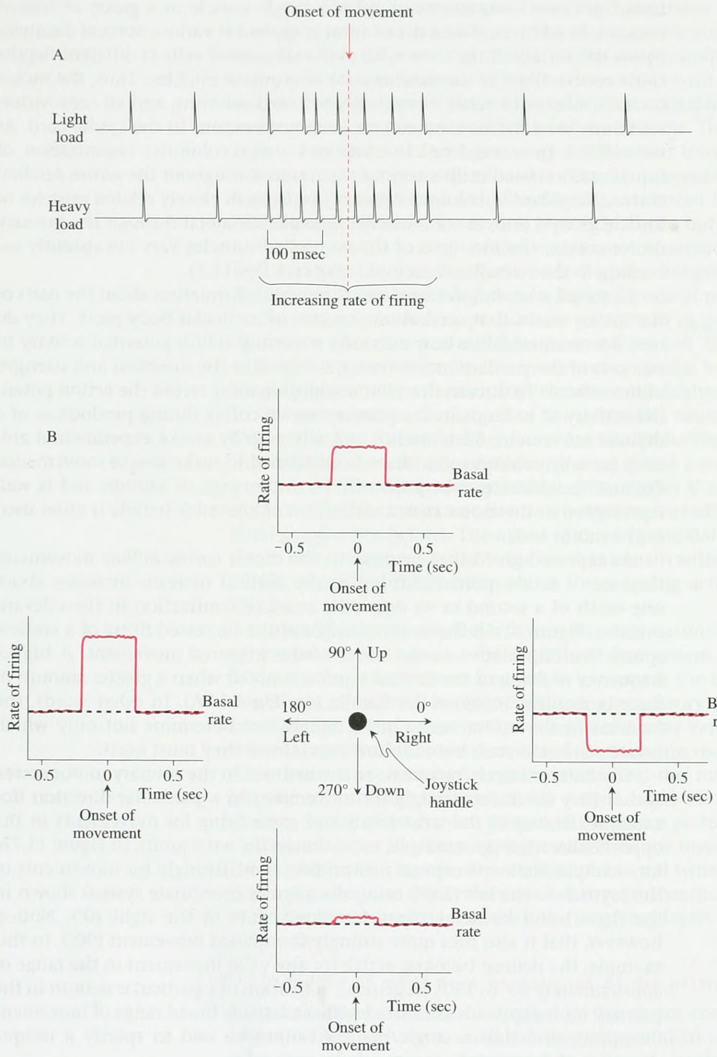
Electrical stimulation can be applied to the motor cortex using microelectrodes, which activate a small number of pyramidal neurons in a specific subregion of the motor cortex and at different depths within the cortex. Information can then be gathered to map motor control at a finer level of detail than can be obtained by placing large stimulating electrodes on the cortex surface. Using this technique, individual cortical neurons have been found to cause contractions in either a single muscle or a group of related muscles. In addition, when stimulation is applied at various vertical distances below the surface of the cortex, all of the stimulated cells at different depths cause contractions in the same muscle or group of muscles. Thus, the motor cortex consists of a series of vertically oriented columns, and all cells within a column have similar connections to motor neurons in the spinal cord. As we will see in more detail in chapter 17, this columnar organization of functionally related cells is commonly found throughout the entire cerebral cortex. Neighboring columns cause contraction in closely related muscles or muscle groups, and, as we move from medial to lateral through the primary motor cortex, the locations of the controlled muscles vary consistently according to the overall somatotopic map (see Fig. 11.5).

Electrical stimulation experiments provide information about the parts of the motor cortex that control movements of particular body parts. They do not, however, establish how normally occurring action potential activity in neurons of the primary motor cortex is related to the direction and strength of movement. To discern this relationship, we must record the action potential activity of neurons in the primary motor cortex during production of a defined movement. Such studies typically employ awake experimental animals (usually monkeys) that have been trained to make simple movements. Because the primate wrist joint offers a wide range of motion and is well represented in the motor cortex, deflection of a joystick handle is often used as the motor task.

As expected given that neurons in the motor cortex *initiate* movement, the rate of action potential firing in the cortical neurons increases about one-tenth of a second or so *before* the onset of contraction in the relevant muscles. Figure 11.7A shows an example of the increased firing of a cortical spinal neuron, relative to the onset of the triggered movement. A higher frequency of firing of the cortical neuron is noted when a greater amount of force is required to move the handle (see Fig. 11.7A). In other words, the neurons in the motor cortex send signals that determine not only which muscles are activated, but also how much force they must exert.

One interesting characteristic of the neurons in the primary motor cortex is that they fire most strongly for movements in a particular direction (for example, flexion of the wrist joint) and cease firing for movements in the opposite direction (for example, extension of the wrist joint). In Figure 11.7B, for example, the corticospinal neuron fires most strongly for movements of the joystick to the left (180°, using the angular coordinate system shown in the figure) and becomes silent for movements to the right (0°). Notice, however, that it also fires quite strongly for upward movement (90°). In this example, the neuron becomes active for any wrist movement in the range of approximately 90° to 180°. In general, activation of a particular neuron in the primary motor cortex is associated with a relatively broad range of movement directions, and thus a single neuron cannot be said to specify a unique direction of movement.

How might the direction of movement be specified? The direction of movement for a limb is thought to depend on the overall pattern of activity in the entire population of corticospinal neurons controlling the relevant


A
Onset of movement
Light load
Heavy load
100 msec
Increasing rate of firing
B
Rate of firing
Basal rate
−0.5
0
0.5
Time (sec)
Onset of movement
90° Up
180° Left
0° Right
270° Down
Joystick handle

muscles. Recording from the entire population of cortical neurons that control the wrist, for instance, might identify some neurons that fire strongest for upward movements, some for movements down, some for motion to the right, and some for movement to the left. In the population of cells, all preferred directions from 0° to 360° would be represented. The pattern of the firing frequency in the population will vary, depending on the intended direction of movement, as shown in Figure 11.8. For a movement direction of 180°, the cells whose preferred direction is 180° will be most strongly stimulated, while those whose preferred direction is 0° will be most strongly inhibited (black curve in Figure 11.8). Cells with intermediate preferred directions will be less strongly affected. This pattern of activity in the corticospinal inputs to the spinal cord will then most strongly activate the spinal motor neurons controlling muscles that move the wrist joint to the left (that is, 180°). For an intended movement direction of 90°, the pattern of activity in the cell population will shift to that shown by the red curve in Figure 11.8. Thus, the pattern of excitation reaching the spinal motor neurons will shift, and a different set of muscles controlling the wrist joint will be most strongly activated.

This model provides a simplified representation of the rather complex and poorly understood actions of the corticospinal system in the spinal cord. Nevertheless, it should serve to demonstrate that the encoding of movement direction is a population characteristic of the cortical neurons, rather than being uniquely determined by a small group of cells.

Other cortical areas involved in motor control

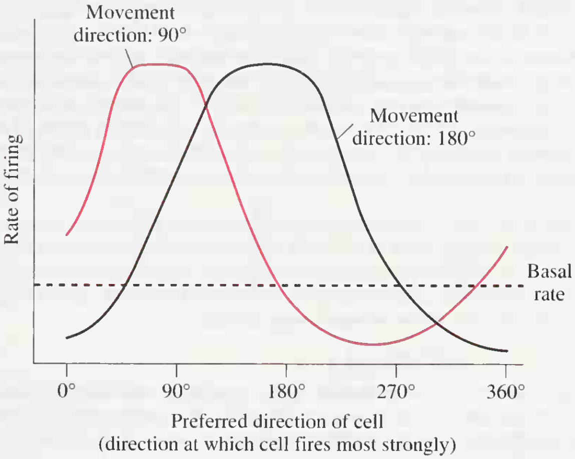
Electrical stimulation of the precentral gyrus produces well-defined movements of particular muscles or muscle groups, with the topographical organization described earlier (see Fig. 11.5). Stimulation of other parts of the brain also produces movement.

Brodmann's cortical area 6 lies just anterior to the primary motor cortex, and electrical stimulation applied in this area has been found to elicit movements. In addition, pyramidal neurons in area 6 send axons both to the primary motor cortex and down to brainstem and spinal cord motor circuits, indicating that they exert both direct influence on lower motor centers and

Figure 11.7

The firing characteristics of corticospinal neurons in the primary motor cortex. (A) An example of action potential activity in a cortical neuron. The time of onset of the neuron-triggered movement is indicated by the arrow and dashed vertical line. The upper trace shows the activity when the muscle must move a light load, and the lower trace shows the activity when the muscle must move a heavy load. (B) The firing rate of a corticospinal neuron depends on the direction of movement. The diagram in the center shows the directions of motion of a joystick handle, which is deflected by movements of the wrist joint. The four graphs indicate the changes in the firing rate of a particular neuron in the part of the motor cortex controlling the wrist joint. This neuron fires most strongly for movements to the left, but also fires prior to upward movements. The firing rate falls below the basal level of spontaneous firing for movements to the right. Downward movements are associated with little change in the firing rate.

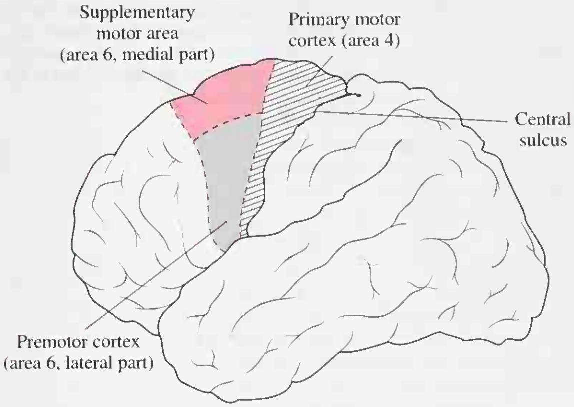
Figure 11.8
The pattern of action potential activity in the entire population of corticospinal neurons controlling the wrist joint. The *x*-axis shows the preferred direction for the cells making up the population (that is, the direction of movement at which the firing rate for a given cell is highest). The black curve shows the pattern of firing in the population for movement of the joystick handle to the left (180° in Figure 11.7B). The red curve shows the pattern of activity for upward movement (90°).



indirect influence via the primary motor cortex. Figure 11.9 shows the location of these additional cortical motor regions in the human brain.

Area 6 is divided into two functionally distinct regions: the **supplemental motor area**, which is located more medially, and the **premotor cortex**, which is located laterally. The movements produced by stimulation of area 6 tend to be more complex than the discrete muscle movements evoked by stimulation of area 4. For instance, area 4 stimulation might cause movement of a single finger, while stimulation in area 6 might produce coordinated movement of all fingers on the hand. Consequently, the supplemental motor area and the premotor cortex are thought to be used in programming sequences of movements and in integrating sensory information with motor commands so that movements of limbs and the body produce actions that "make sense" within the environment. Exactly how the neurons of these cortical regions interact with one another and with the neurons of area 4 to program and implement an appropriate plan of action on a moment-by-

Figure 11.9
The location of the supplementary motor area (red) and the premotor cortex (shaded gray) in cortical area 6. The primary motor cortex is cross hatched.


Supplementary motor area (area 6, medial part)
Primary motor cortex (area 4)
Central sulcus
Premotor cortex (area 6, lateral part)

moment basis remains poorly understood. Nevertheless, it is clear that lesions in area 6 interfere with the ability to make complex coordinated movements in primates.

THE BASAL GANGLIA

Although the cerebral cortex is the most prominent and visible forebrain structure, other more hidden parts of the forebrain are also important in motor control. In the central part of the telencephalon are three interconnected groups of neurons, collectively called the **basal ganglia.** Their locations are shown schematically in Figure 11.10. The three groups are the **caudate nucleus**, the **putamen**, and the **globus pallidus.** Together, the caudate nucleus and the putamen are known as the **striatum.**

Unlike other motor systems we have discussed so far, the basal ganglia have no direct connections with either the spinal cord motor control systems or the brainstem motor centers. Instead, they exert their motor effects principally by altering the output of cortical motor areas—albeit indirectly. The basal ganglia do not themselves project directly to the motor cortex; instead, they influence the parts of the thalamus that in turn provide inputs to the motor cortex (Fig. 11.10B). Thus, the basal ganglia monitor the output from the motor cortex (via the corticostriatal connections) and control the inputs

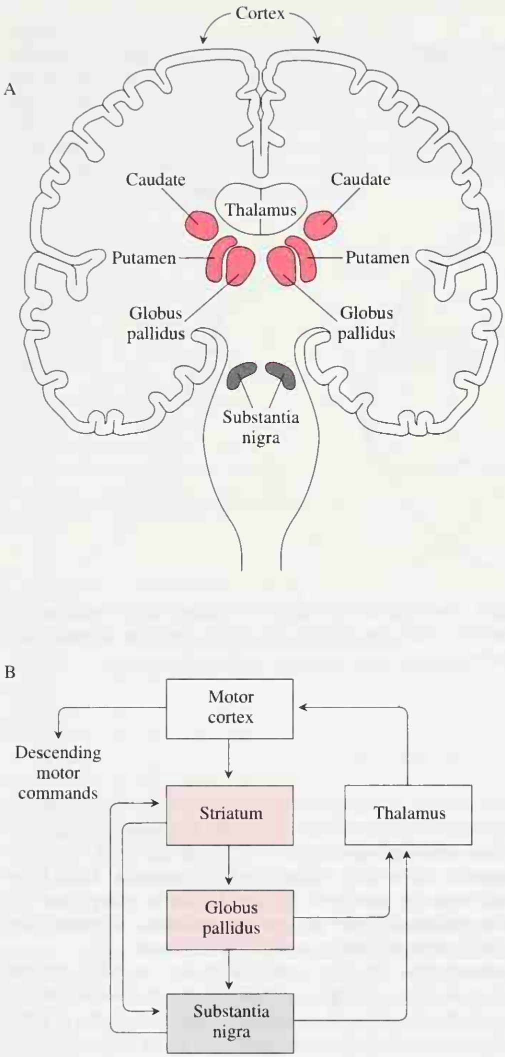


Figure 11.10
The organization of the basal ganglia. (A) The approximate locations of basal ganglia within the core of the forebrain. The three nuclei of the basal ganglia (caudate, putamen, and globus pallidus) are arrayed around the thalamus. The substantia nigra is located in the midbrain. (B) Connections of the basal ganglia (red) and substantia nigra (gray). The striatum consists of the caudate and putamen.

that generate activity in the voluntary motor output path. In keeping with this central position in the motor command pathway, defects in the basal ganglia are associated with severe deficits in motor behavior.

Another brain region intimately associated with the basal ganglia is the **substantia nigra**, which is located in the midbrain (see Fig. 11.10A). Many neurons of the substantia nigra contain high concentrations of the neurotransmitter dopamine, which oxidizes to form a dark pigment in freshly cut brain sections. This pigment makes the area appear black, giving rise to the name of the nucleus. As diagrammed in Figure 11.10B, the substantia nigra both receives inputs from and sends outputs to the striatum. In addition, some parts of the substantia nigra project to the same thalamic nuclei that relay the outputs from the basal ganglia to the motor cortex. Although the synaptic inputs from the substantia nigra to the striatum release the neurotransmitter dopamine, the substantia nigra neurons that project to the thalamus use the neurotransmitter GABA. Exactly how these synaptic inputs alter motor commands is not yet understood in detail.

Degeneration of the dopamine-releasing neurons of the substantia nigra destroys the synaptic inputs to the striatum, severely impairing motor activity. In humans, degeneration of the substantia nigra neurons leads to **Parkinson's disease**, a condition associated with muscle tremor and difficulty in initiating and sustaining locomotion. Thus, the dopamine-releasing neurons of the substantia nigra seem to be important in the translation of motor plans into actual motor commands.

THE CEREBELLUM

We will now return to the brainstem to discuss another of the major motor system components in the brain: the cerebellum. The cerebellum forms an evagination of the midbrain on the dorsal surface of the brain at the level of the pons (Fig. 11.11). Although its size varies across animal species, in mammals it is a major brain structure and plays important roles in sensorimotor integration. From its strategic position astride the ascending sensory pathways and descending motor pathways in the brainstem, the cerebellum monitors both sensory and motor information and provides feedback control of motor outflow.

One of the main sensory inputs to the cerebellum comes from sensory systems that give information about the orientation and the acceleration of the body during locomotion. These information sources include the vestibular apparatus and, in fish, the lateral line system (which provides input related to water movement over the body surface). The cerebellum appears to have evolved as an adjunct to the brainstem locomotor command centers involved in swimming, for the purpose of adjusting motor commands based on sensory feedback about the organism's position in space. In terrestrial animals, additional sensory information about joint position, muscle length, and muscle tension must also be monitored to fine-tune motor output based

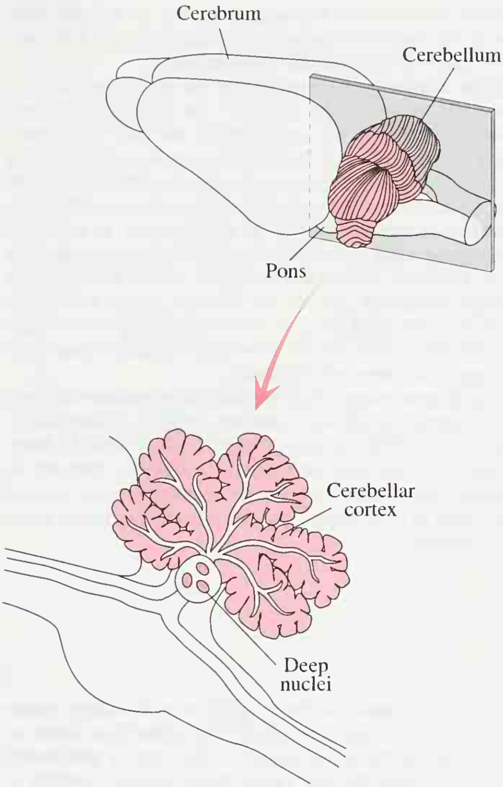


Figure 11.11
The location of the cerebellum in the brainstem. The three-dimensional view (above) represents the cerebellum and cerebrum of a rodent brain. The cross section (below) shows the division of the cerebellum into the deep nuclei and the cerebellar cortex.

on performance. With the evolution of forebrain motor control systems, the cerebellum was required to monitor additional motor commands and to send outputs to additional target areas. These evolutionary developments are associated with the expansion of the brain tissue devoted to the cerebellar circuitry.

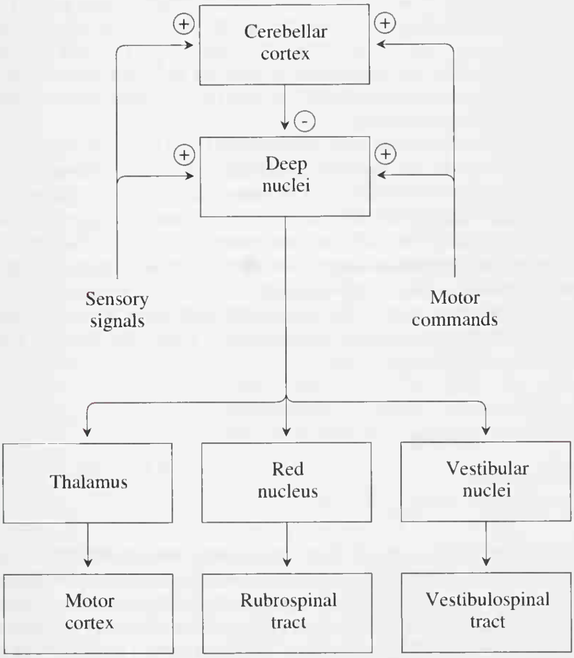
In keeping with the idea that the cerebellum modulates motor output to make fine adjustments based on performance, lesions of the cerebellum do not prevent movement but do interfere with balance and coordination. As a result, movements become awkward and less effective.

In vertebrates with a well-developed cerebellum, the cerebellum consists of two highly convoluted hemispheres overlying the brainstem, and three pairs of **deep nuclei** hidden within. The deep nuclei are called the **dentate nucleus**, the **emboliform nucleus**, and the **fastigial nucleus.** The cerebellar hemispheres have an organization analogous to that of the cerebral hemispheres, with a densely packed cellular layer (the cerebellar cortex) on the outside and white matter containing incoming and outgoing axons underneath.

The deep nuclei receive synaptic inputs from two types of axons: those carrying sensory information and those carrying information about motor commands being issued from both cortical and brainstem sources. This information is also sent to the cerebellar cortex for further processing. The neurons of the cerebellar cortex receive synaptic inputs from neurons that are part of sensory systems as well as neurons that are part of motor systems. As a result, the cerebellar cortex can compare motor commands with sensory information of various kinds. The processed output from the cerebellar cortex is then relayed back to the deep nuclei. This information flow is diagrammed in Figure 11.12. The exact nature of the calculation being performed in the

Figure 11.12

Connections of the cerebellum. Excitatory connections are indicated with a ⊕ and inhibitory connections are indicated with a ⊖.



deep nuclei has not yet been unraveled, and it remains unknown exactly how the sensory and motor signals are combined and compared in the cerebellar cortex. In general, however, the information flow shown in Figure 11.12 seems well suited to a comparison, carried out in the deep nuclei, between an outgoing motor command and an altered form of the motor command that has been passed through the neuronal network of the cerebellar cortex. Note also that the incoming axons make excitatory synapses onto the neurons of the deep nuclei, while the sole output from the cerebellar cortex, leading back to the deep nuclei, consists of inhibitory synapses onto the neurons of the deep nuclei.

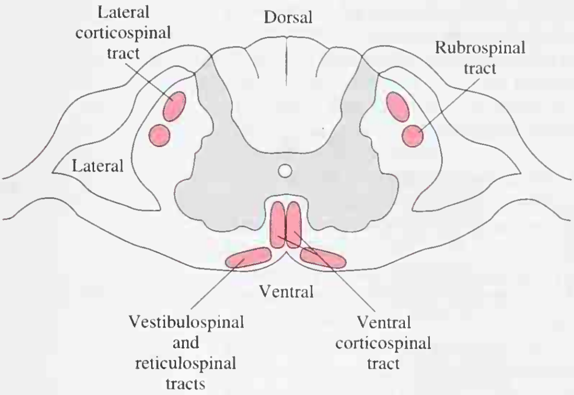
The outputs from the cerebellar deep nuclei project to all of the brain motor systems (see Fig. 11.12), as might be expected for a structure that is involved in modulating motor performance. The vestibular nuclei provide a major sensory input to the cerebellum, giving information necessary to maintain balance and body posture during locomotion. The cerebellum sends outputs back to the vestibular nuclei to regulate the outputs of the vestibulospinal motor system. The red nucleus also receives major output from the cerebellum, which helps control the activity of the rubrospinal motor system. Likewise, the cortical motor system is also targeted by the outputs of the cerebellum. As with the basal ganglia, the cerebellum exerts an indirect effect on the motor cortex. The cerebellar deep nuclei project to the thalamus—including the same thalamic nuclei that receive inputs from the basal ganglia—and the thalamus in turn sends inputs to the cortical motor areas. In this way, the cerebellum influences both the corticospinal and corticobulbar motor systems indirectly, via the thalamic neurons that provide inputs to the motor cortex.

The cerebellum is thought to play an important role in motor learning—the process by which the timing and amplitudes of motor commands are altered based on experience with prior motor outcomes. The pattern of sensory and motor connections to and from the cerebellum appears to be well suited to such a role. The wide range of sensory inputs received by the cerebellum provides information about the sensory consequences of motor acts, and the cerebellum also receives inputs from motor centers related to their outgoing motor commands. The role of the cerebellum in motor learning will be discussed in more detail in chapter 21, when we consider how reflexes can be modified.

ORGANIZATION OF DESCENDING MOTOR TRACTS IN THE SPINAL CORD

The principal target of the outputs from brain motor areas is ultimately the spinal cord. The motor neurons that control most of the somatic musculature are located in the gray matter of the spinal cord, and the brain motor systems must eventually connect with these motor neurons to affect the activity of those muscles. The descending axons from the brain form a large portion of

Figure 11.13
The location in the spinal cord white matter of the descending axon tracts from the brain motor control areas.


Lateral corticospinal tract
Dorsal
Rubrospinal tract
Lateral
Ventral
Vestibulospinal and reticulospinal tracts
Ventral corticospinal tract

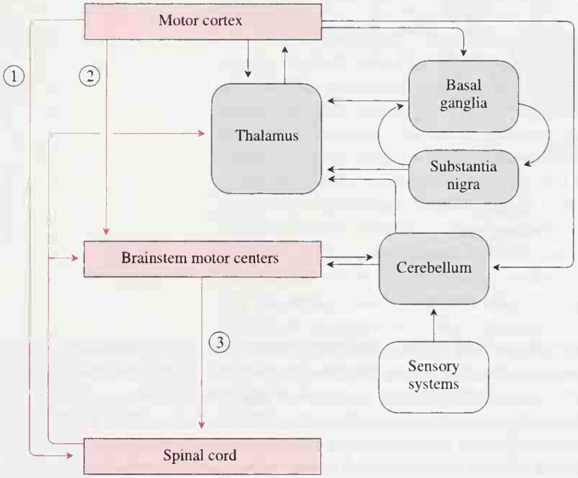
the white matter of the spinal cord (see chapter 10), with ascending sensory axons accounting for the remainder (see chapter 15). The axons coming from each brain motor region travel together in discrete bundles, or tracts, that occupy characteristic positions in the spinal cord white matter. Figure 11.13 shows the organization of these tracts. The axons from the motor cortex form two tracts: the **lateral corticospinal tract** in the lateral portion of the white matter, and the **ventral corticospinal tract** in the medial portions of the ventral white matter. The axons of neurons in the red nucleus (the **rubrospinal tract**) also descend in the lateral portion of the white matter (see Fig. 11.13), near the area occupied by the lateral corticospinal tract. The vestibular nuclei and the reticular formation in the brainstem give rise to descending fibers that occupy ventral portions of the white matter (see Fig. 11.13).

As the tracts from all of the higher motor centers descend in the spinal cord, axons leave the tracts and enter the gray matter. There, synaptic connections are made either directly onto motor neurons or onto spinal interneurons that then affect the activity of the motor neurons.

SUMMARY

Now that we have discussed the major components of the motor control system of the brain, we can return to our summary diagram (see Fig. 11.1) and add some of the functional interconnections described in this chapter. In the more detailed block diagram in Figure 11.14, the hierarchical core of

Figure 11.14
A summary of the interconnections of the brain motor control systems. The central hierarchy is shaded red. Arrow 1 is the corticospinal tract, arrow 2 is the corticobulbar tract, and arrow 3 represents the reticulospinal, vestibulospinal, and rubrospinal tracts. Brainstem motor centers and cortical motor areas are grouped together into single boxes to simplify the wiring diagram. The connection from the cortex to the cerebellum is indirect via brainstem relay nuclei.



the motor outflow path (consisting of the motor cortex, the brainstem motor centers, and the spinal cord) is shaded red. Ascending sensory information about muscles and joints is distributed to the brainstem and the thalamus. At the top of the hierarchy lies the motor cortex. For simplicity, we have lumped together the primary motor cortex, supplementary motor cortex, and premotor cortex (see Fig. 11.9) in a single box in Figure 11.14. Bear in mind that each of these cortical motor areas has its own set of interconnections and its own motor functions. In general, the primary motor cortex (cortical area 4) produces discrete movements of single muscles or related groups of muscles, while the supplementary motor area and premotor cortex (cortical area 6) produce more global movements of larger body regions.

Two main tracts of axons descend from the motor cortex: the corticospinal tract (labeled 1 in Figure 11.14) and the corticobulbar tract (labeled 2 in Figure 11.14). The axons in these tracts originate from neurons called pyramidal cells found in layer V of the cortex (see Fig. 11.6). The descending axons from the brainstem motor centers to the spinal cord (labeled 3 in Figure 11.14) are subdivided into three major groups. First, the reticulospinal tract originates in the reticular formation of the brainstem and makes synaptic connections onto motor neurons and interneurons throughout the spinal cord. Excitatory inputs in the spinal cord from reticulospinal neurons in the brainstem drive the central pattern generators of the spinal cord to initiate locomotion. Second, the vestibulospinal tract originates in the vestibular nuclei of the brainstem. Activation of this tract promotes extension of the limbs and inhibits flexion. Third, the rubrospinal tract originates in the red nucleus. Activation of this tract promotes flexion of the limbs and inhibits extension. The balance of activity in the vestibulospinal system and the rubrospinal system is therefore important in governing the flexion/extension equilibrium of the limbs.

In addition to the hierarchically arranged central core of the motor pathways, other components monitor and regulate the motor commands to coordinate movements based on ongoing sensory information. These regulatory regions (shaded gray in Figure 11.14) are also important in initiating motor commands during voluntary movements. The basal ganglia in the forebrain receive inputs from the motor cortex and project back to the motor cortex indirectly via the parts of the thalamus that send axons into the motor areas of the cortex. The basal ganglia are divided into the globus pallidus and the striatum, with the latter consisting of the caudate nucleus and the putamen. The basal ganglia are also closely associated with a midbrain region called the substantia nigra.

Together with the thalamus, the basal ganglia and substantia nigra produce three interconnected feedback loops that affect the cortical motor areas. To trace these loops, follow the arrows among nuclei to form circular paths. First, a local feedback loop goes from the basal ganglia to the substantia nigra and then back to the basal ganglia. Second, a loop circles from the motor cortex, to the basal ganglia, to the thalamus, and then back to the motor cortex. A slightly longer path exists from the motor cortex, to the basal ganglia, to the substantia nigra, to the thalamus, and then back to the motor cortex. These interrelated feedback loops allow the basal ganglia and the substantia nigra, acting via the thalamus, to influence the motor outputs from the cortex. The importance of these connections is evident in Parkinson's disease, in which humans experience problems in the initiation of movement after dopamine-containing neurons of the substantia nigra are destroyed.

The other important brain component involved in motor coordination is the cerebellum, which is part of the brainstem. It consists of two principal divisions: the deep cerebellar nuclei and the cerebellar cortex. Both of these regions receive sensory information from a variety of sensory systems, as well as copies of the motor commands sent by the cortical and brainstem motor centers. The deep nuclei then feed information back to these motor centers. The feedback is direct in the case of the brainstem centers and indirect (via the thalamus) in the case of cortical centers. The cerebellum may have evolved as a brainstem center in fish, where it was responsible for combining vestibulospinal and reticulospinal motor outputs with vestibular information about body position to fine-tune motor commands during swimming. Fine coordination of limb movements and maintenance of balance during locomotion are among the functions of the cerebellum in mammals. The cerebellum also plays a role in motor learning.

Although a great deal is known about the wiring diagram of the brain motor control centers, exactly how the complex interconnected loops (see Fig. 11.14) interact to produce coordinated motor behavior is not yet understood. In some cases, such as the cerebellar cortex, the detailed cell-to-cell synaptic interactions have been well worked out. In other cases, the cellular interactions corresponding to the various arrows shown in Figure 11.14 remain unknown. Unraveling the mysteries of these motor control networks and arriving at a cellular understanding of how they work—at the level of detail we are approaching today with spinal cord systems (see chapter 10)—should continue to challenge generations of neurobiologists to come.

12

Sensorimotor Integration

One feature we have encountered throughout our consideration of spinal cord and brain motor mechanisms is the importance of sensory information. In broad terms, the process by which sensory information becomes converted in the nervous system into appropriate motor action is known as **sensorimotor integration.** We have already seen several examples of sensorimotor integration. In the spinal cord, the reflexes we have considered are triggered by specific events that are detected by specialized sensory receptor neurons. The synaptic connections made by those sensory neurons within the spinal cord then determine exactly which motor neurons become activated and which inhibited to generate the reflex response. In the stretch reflex (myotatic reflex), for instance, the group Ia sensory neurons innervating the muscle spindles make monosynaptic excitatory connections with the motor neurons of the same muscle. Through this very simple but elegant synaptic arrangement, sensory information (in this case, that the muscle has been passively stretched) is integrated within the spinal cord to produce the desired motor consequences (contraction of the muscle to oppose the passive stretch). Even in the case of more complex reflexes, such as the withdrawal reflex (chapter 10), the pattern of synaptic connectivity within the spinal cord can account in a rather straightforward way for the translation of sensory information into motor commands.

For brain motor mechanisms, the rules that govern sensorimotor integration are less clear. Sensory information reaches these systems for the most part only after passing through numerous synaptic relay stages. In general, the synaptic processing is more complex and the calculations and transformations performed at each relay stage are less well understood than is the case for spinal reflexes. Nevertheless, good progress has been made toward understanding the translation of sensory information into motor output within the brain in a few specific systems, including the one that controls the movements of the eyes—the **oculomotor system.** This chapter will explore several aspects of the oculomotor motor system as a model for understanding sensorimotor integration in the brain.

As a model system, eye movements provide several advantages. First, human beings are highly visual animals, and so students of neurobiology (and research neurobiologists) have an intuitive comprehension of many of the neuronal phenomena under investigation. Second, the relevant sensory pathways (visual system and vestibular system), although complex, have been widely studied and good information is available about the sensory side of the control pathways. Third, the complement of muscles that produce the coordinated movements of the eyes is relatively small, and thus the number of motor neuron pools is rather limited, simplifying the neurophysiological analysis. In addition, the object being moved—the eyeball—is not a limb or skeletal joint, and so the motor control mechanisms do not have to compensate for widely varying amounts of load on the muscles, unlike the motor systems regulating joint movements. This fact further simplifies the analysis. Finally, because the oculomotor system incorporates both reflexive and voluntary movements, we can examine contributions from both cortical and subcortical control systems. We will begin by considering reflexive eye movements, and then describe some properties of the voluntary control mechanisms.

REFLEXIVE EYE MOVEMENTS: VESTIBULO-OCULAR REFLEX

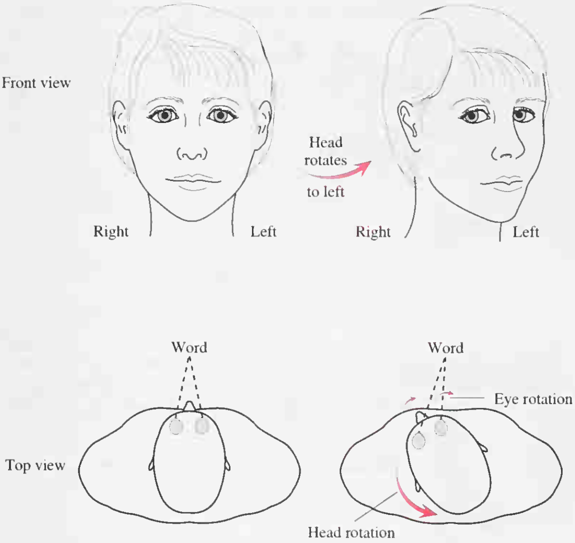
As we walk, the position of our heads—and thus the position of our eyes—is constantly shifting in three-dimensional space. Despite this movement, the world does not appear to shift and blur as we move, and we have no trouble maintaining a constant view of it. The control system that keeps the eyes pointed in the same direction in external space in the face of large rotations of the head is the **vestibulo-ocular reflex** (VOR). It is easy to demonstrate the operation of this system on yourself as you are reading these words. Focus on this *word* in this sentence, and slowly rotate your head first to the right and then to the left. You should be able to keep the word in sharp focus during the rotation. Do the same while rotating your head vertically, instead of horizontally. If you repeat this exercise while focusing on the reflection of your own eyes in a mirror, you will readily see the large changes in eye position within the orbit that occur to keep the fixated object in the center of the field of view (Fig. 12.1A). The direction of eye motion takes place in the opposite direction from head motion, as required to keep the eyes pointed at the same location in space.

The sensory information used to control the eye movements in these examples could, in principle, derive from the visual system. That is, a shift in image position on the retina could generate an error signal to be passed to the motor neurons controlling the eye muscles, producing a compensating movement to cancel the image shift. Indeed, visual information is used in this way to help position the eyes, as we will discuss later in this chapter. In the case of horizontal and vertical rotations of the head, however, the sensory signals come from the parts of the vestibular apparatus that are sensitive to rotation: the semicircular canals. To see how this reflex works, we must become familiar with the eye muscles and their neuronal control, as well as the vestibular apparatus.

The eye muscles and their motor neurons

The eyes of most vertebrates are capable of four types of motion, summarized in Figure 12.2. The eye can be moved to the left and right in the horizontal plane and up and down in the vertical plane. In addition, it can be rotated in the eye socket, and it can be retracted into the socket (for example, when

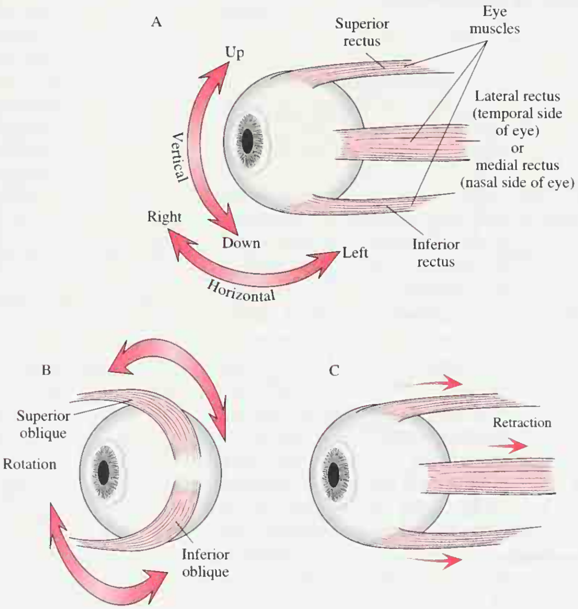
Figure 12.1
The vestibulo-ocular reflex keeps the eyes directed toward the same point in space as the head rotates. (Top) A frontal view, similar to what you would see if you looked at your own reflection in a mirror while turning your head to the side. (Bottom) A schematic top view, showing that the eyes change position in the appropriate way to keep light from the external world on the same portion of the retina at the back of the eyes.



the eyes are tightly closed in anticipation of a blow). The exact arrangement of the muscles necessary to achieve these movements varies across species, depending on the anatomy of the eye socket and on the relative importance for the animal of each type of motion. In humans, the first two motions (horizontal and vertical) are the most important in stabilizing the visual world during head rotation.

The muscles that move the human eye (the **extraocular muscles**) are shown in Figure 12.2. The **superior rectus muscle** attaches at the top of the eyeball; its contraction produces upward movement. The antagonist of this muscle is the **inferior rectus**, which attaches at the bottom of the eyeball and produces downward rotation when it contracts. Horizontal movements are produced by a pair of muscles that attach to the eyeball on its sides. The **medial rectus muscle** attaches on the side toward the nose and produces horizontal rotation toward the nose; the **lateral rectus muscle** attaches on the side of the eyeball toward the side of the head and produces horizontal

Figure 12.2
The organization of the extraocular muscles. The six muscles are arranged to pull the eye in various directions. (A) The four rectus muscles move the eyes in the vertical and horizontal planes. (B) The two oblique muscles rotate the eye. (C) Acting in concert, all of the muscles can retract the eye into the socket for protection.

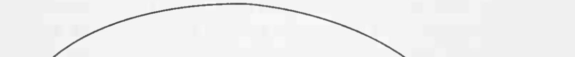


rotation away from the nose. Rotation of the eye in the socket is controlled by another pair of opposed muscles, called the **superior oblique** and **inferior oblique muscles.** The extraocular muscles fan out and form fairly broad insertions on the surface of the eyeball (see Fig. 12.2). These insertions are not precisely located at the horizontal and vertical meridians of the eyeball, and so all of the individual muscles produce components of motion in both horizontal and vertical axes. For our purposes, however, we can neglect the minor vertical movements produced by the medial and lateral rectus muscles and the minor horizontal movements produced by the superior and inferior rectus muscles.

The extraocular muscles are attached at the other end to a common tendon at the back of the orbit, with the exception of the inferior oblique muscle, which attaches on the nasal side of the orbit. As mentioned in chapter 9, the muscle fibers of the extraocular muscles produce the fastest contractions of all muscles in the body. By activating various combinations of this small set of muscles, the nervous system can rapidly and precisely position the eyes to center the gaze on any portion of the visual field.

Like any other striated muscle, the extraocular muscles are controlled by motor neurons. The motor neurons we have discussed so far (for example, those involved in the patellar reflex) have been located in the spinal cord. In contrast, the motor neurons of the extraocular muscles are located within the brain itself, in the **oculomotor nuclei** of the brainstem. The locations of these nuclei are shown in Figure 12.3. In the spinal cord, the axons of motor neurons exit via the segmental spinal nerves. The segmental organization imposed by the vertebral column is absent in the brain, however. Consequently, the outgoing axons from motor neurons located at levels above the spinal cord exit the brain case (cranium) via a set of nerves called the **cranial nerves**. Humans possess 12 pairs of cranial nerves, which are identified with Roman numerals. Axons of oculomotor neurons are carried in three different cranial nerves. The appropriately named **oculo-**

Figure 12.3
A lateral view showing the approximate anterior–posterior locations of the motor neurons that control the extraocular muscles. The Roman numerals refer to the numbers of the corresponding cranial nerves.


Cerebrum
Superior colliculus
Inferior colliculus
Cerebellum
Oculomotor nucleus (nerve III)
Trochlear nucleus (nerve IV)
Abducens nucleus (nerve VI)

motor nerve (nerve III) carries axons that innervate most of the extraocular muscles, including the superior and inferior rectus muscles, the medial rectus muscle, and the inferior oblique muscle. The superior oblique muscle is supplied via cranial nerve IV (the **trochlear nerve**), while the lateral rectus muscle receives its motor innervation through cranial nerve VI (the **abducens nerve**).

The most anterior of the oculomotor nuclei is the motor nucleus of the oculomotor nerve, which lies near the midline in the midbrain at the level of a protrusion on the dorsal surface of the brainstem called the superior colliculus (see Fig. 12.3). As we will discuss later, the superior colliculus is also involved in the control of eye movements. The motor neurons of the trochlear nerve also lie along the midline of the brainstem, slightly more posterior than the motor neurons of nerve III, at the level of the inferior colliculus. The motor neurons of the abducens nerve are found even further posterior, just beneath the floor of the fourth ventricle.

Like the motor neurons of the spinal cord, the cranial nerve motor neurons are cholinergic, releasing acetylcholine as their neurotransmitter at the neuromuscular junctions onto the extraocular muscles. As a result, the motor neurons in the brainstem can be revealed anatomically by staining with histological methods that detect the presence of the cholinergic synthetic enzyme, choline acetyltransferase (Fig. 12.4).

The semicircular canals

We will now turn to the sensory end of the vestibulo-ocular reflex and examine the structures that pertain to head movement: the vestibular apparatus. Phylogenetically, sensory structures that give information about the position of the animal with respect to gravity and about the acceleration of the animal are among the oldest sensory systems. Such sensory organs are based on a specialized type of sensory cell called the **hair cell** (to be described in detail in chapter 18). Hair cells change their membrane potential in response to deflections of fine cilia that project from one end of the cell, as shown in Figure 12.5. The cilia increase in length from one side of the cell to the other. Deflection of the cilia toward the longest cilium depolarizes the hair cell, while deflection in the opposite direction (away from the longest cilium) hyperpolarizes the hair cell. The amount of depolarization or hyperpolarization depends on the amount of deflection. The hair cell makes a synaptic connection onto a sensory neuron that then projects into the brain. As in other synapses, the hair cell releases more neurotransmitter upon depolarization and stops releasing when it becomes hyperpolarized. Because the neurotransmitter is excitatory for the sensory neuron, the rate of action potentials in the sensory neuron increases when the cilia are deflected in the direction that depolarizes the hair cell and decreases when the cilia are deflected in the opposite direction (see Fig. 12.5).

Sensory organs using hair cells to detect the organism's position with respect to gravity are found universally among multicellular, mobile animals. The basic vertebrate position-sensing organ is the **otolith organ**—essentially

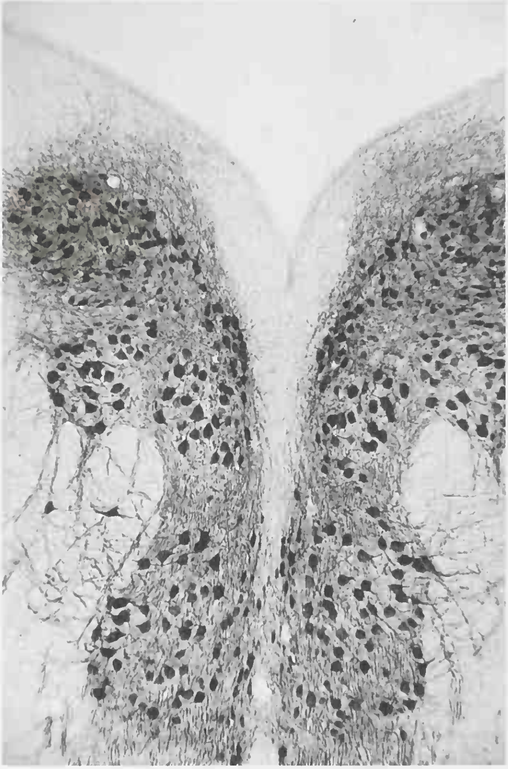


Figure 12.4
Motor neurons of the oculomotor nucleus. The cells were stained by a histochemical procedure to detect choline acetyltransferase, which reveals cholinergic neurons such as the motor neurons.

Courtesy of J. T. Erichsen of the University of Wales.

a closed sack of fluid, with hair cells located on the interior surface. The cilia of the hair cells project into the interior of the sack, where they are embedded in a gel-like material containing tiny crystals of calcium carbonate, called **otoliths** ("ear stones"). The crystals add mass to the gel, allowing the entire structure to shift in response to the pull of gravity when the animal tilts to the side. This is illustrated in Figure 12.6.

When the animal is upright, the gel rests directly over the hair cells, and the cilia lie near their midpoint and are not deflected significantly in either direction. Under these conditions, transmitter is released from the hair cell at a moderate rate, and the sensory neurons that receive synapses from the hair cells fire action potentials at a correspondingly moderate rate. The same rate of firing is observed on both sides of the animal (see Fig. 12.6A). When

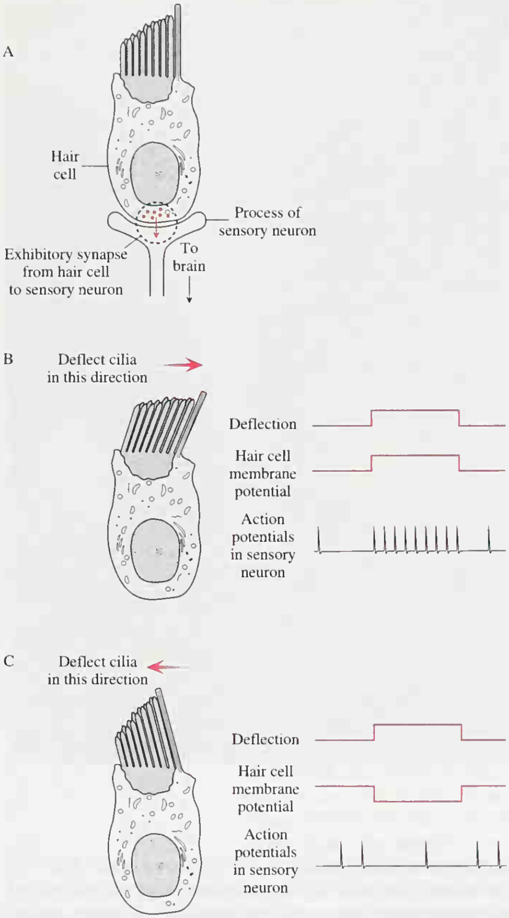
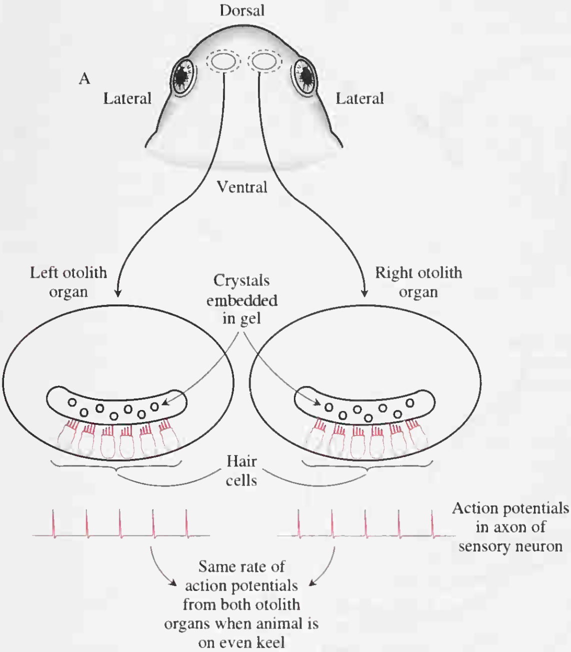

A
Hair cell
Process of sensory neuron
Exhibitory synapse from hair cell to sensory neuron
To brain
B
Deflect cilia in this direction
Deflection
Hair cell membrane potential
Action potentials in sensory neuron
C
Deflect cilia in this direction
Deflection
Hair cell membrane potential
Action potentials in sensory neuron

Figure 12.5
The response of a hair cell to deflection of the cilia. (A) Changes in the membrane potential of the hair cell lead to changes in the release of excitatory transmitter at a synapse between the hair cell and the process of the sensory neuron that connects the hair cell to the brain. (B) The response when cilia are deflected toward the longest cilium. The traces to the left show the deflection, the change in membrane potential of the hair cell, and the action potentials in the sensory neuron. Each upward tick in the sensory neuron trace indicates the occurrence of an action potential. (C) The response when the cilia are deflected away from the longest cilium. In this case, the hair cell hyperpolarizes and the rate of action potentials in the sensory neuron decreases.

the animal tilts to the right, however, both otolith-containing gels shift to the right (see Fig. 12.6B). Because the two otolith organs are mirror images of one another, this movement deflects the cilia in the left-side otolith organ toward the longest cilium in each hair cell; on the right side, the cilia are deflected in the opposite direction, toward the shortest cilium. The result is a depolarization of the hair cells on the left and a hyperpolarization of the

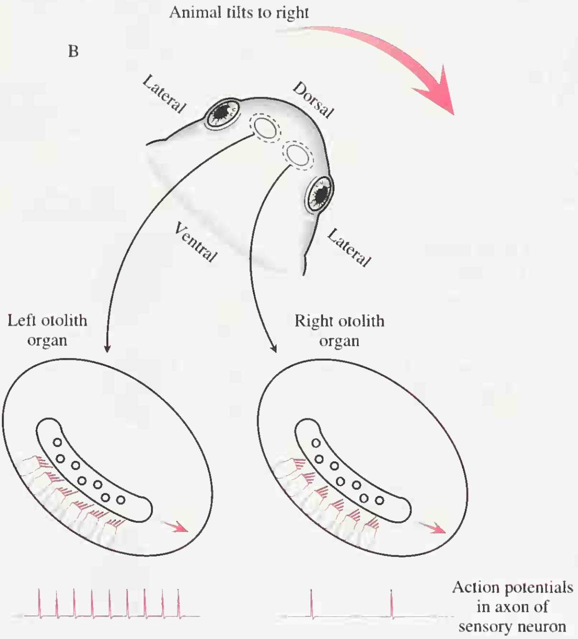
Figure 12.6
The response of sensory neurons of the otolith organs when a primitive vertebrate is tilted. (A) When the animal is level, the otoliths rest evenly on top of the hair cells. The sensory neurons from the otolith organs on both sides fire action potentials at the same, steady rate.


Dorsal
A
Lateral
Lateral
Ventral
Left otolith organ
Crystals embedded in gel
Right otolith organ
Hair cells
Action potentials in axon of sensory neuron
Same rate of action potentials from both otolith organs when animal is on even keel

hair cells on the right. The increased release of excitatory neurotransmitter on the left side increases the rate of action potentials in the sensory neurons on that side. Conversely, the rate of action potentials in the right-side sensory neurons declines. By comparing the rate of action potentials on the two sides, the nervous system can readily determine the relative tilt of the body in space.

The hair cells of the otolith organs provide a steady signal during sustained tilting. As long as the tilt persists, the situation shown in Figure 12.6B will prevail. Note that the same shift in the cilia could be obtained if the animal remained upright but moved at a constant velocity to the left. Thus, the otolith organs give information about static tilt and about constant

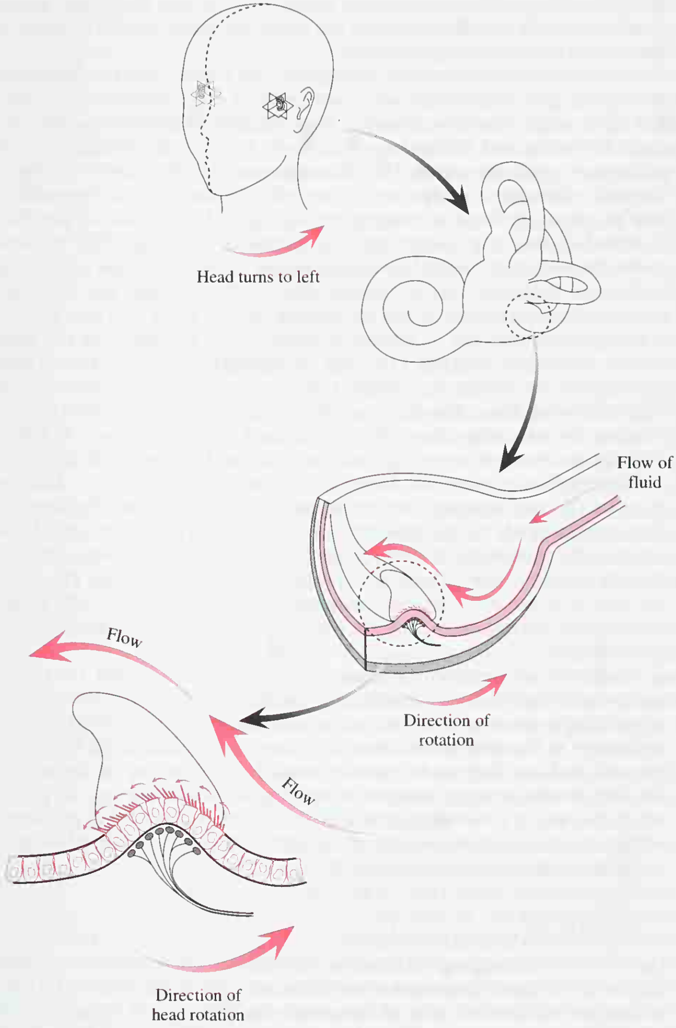
Figure 12.6 (continued)
(B) When the animal tilts to the right, the otoliths shift as indicated. The cilia of the hair cells deflect in opposite directions, relative to the longest cilium. In this case, the hair cells on the left depolarize and those on the right hyperpolarize. The sensory neurons on the left fire action potentials more frequently, while those on the right fire less frequently.



velocity. In humans, as in most other vertebrates, the otolith organs are divided into two parts: one oriented horizontally (the **saccule**) and the other oriented vertically (the **utricle**).

During the course of vertebrate evolution, the simple otolith organ became more elaborate and gave rise to two additional fluid compartments: the **cochlea** and the **semicircular canals**. The otolith organs, the cochlea, and the semicircular canals are collectively called the **labyrinth** (Fig. 12.7). The cochlea first appeared in amphibians and is responsible for the sense of hearing in terrestrial vertebrates (see chapter 18). The semicircular canals form three loops, oriented at right angles with respect to one another. The horizontal plane of the head contains a loop, the vertical plane includes a

Figure 12.7
The response of the semicircular canals to rotation of the head. When the head turns to the left, the labyrinth rotates, setting up a counterflow in the endolymph fluid within the canal. This flow deflects the cupula with the ampulla of the canal, which deflects the cilia of the hair cells and alters the rate of action potentials in the sensory neurons contacted by the hair cells.



second loop, and the anterior-posterior plane contains a third loop. The semicircular canals provide information about the rate of change of the velocity of the head (that is, acceleration). To see how the semicircular canals are sensitive to acceleration, examine the diagrams in Figure 12.7, which illustrate the situation for rotation of the head in the horizontal plane. Similar behavior would be seen for the other two canals during rotation in their respective planes of orientation.

Each semicircular canal is a tube filled with a fluid called **endolymph.** When the head rotates, the solid outer wall of the canal rotates as well. The fluid inside the tube, however, does not immediately follow suit. Because of inertia and its fluid properties, the endolymph initially stays in place when the tube rotates. This discrepancy effectively creates motion of the fluid with respect to the wall of the tube, in the direction opposite to that in which the head is rotating (see Fig. 12.7). This motion of the fluid is sensed by hair cells located inside a specialized swelling, called the **ampulla,** located at the end of each semicircular canal, where the canal joins with the utricle. The cilia of the hair cells in the ampullae are imbedded in a gelatinous structure called the **cupula,** which sticks out into the endolymph from the wall of the canal, like a sail in the wind. As the head rotates, the cupula is dragged through the endolymph, forcing endolymph up and over the cupula. This deflects the cupula and the imbedded cilia of the underlying hair cells (see Fig. 12.7). Depending on the direction of rotation, the hair cells will be either depolarized or hyperpolarized. In Figure 12.7, the deflection is toward the longest cilium and the hair cells depolarize during the head movement. As with the otolith organ, the rate of action potentials in the neurons that contact the hair cells changes. Because the semicircular canals on the two sides of the head are mirror images of one another, the directions of endolymph flow over the cupula will differ on the left and right sides. Therefore, as with the otolith organs (see Fig. 12.6), the rate of action potentials in the vestibular sensory neurons will always increase on one side and decrease on the other side during rotation in a given direction.

If rotation continues in the same direction at the same speed, the inertia in the endolymph fluid is overcome and the fluid inside the canal eventually moves at the same speed as the wall of the canal. When the fluid and the wall move at the same speed, there is no flow of the endolymph relative to the wall, and thus the cupula is not deflected. For this reason, the signal from the semicircular canals is strongest at the onset of rotation, during the period when the head is accelerating from rest. As a result of the physical properties of the detection apparatus within the semicircular canals, the signal progressively declines during sustained rotation.

Translating vestibular information into oculomotor output

How does the sensory signal from the semicircular canal connect appropriately with the motor neurons controlling the extraocular muscles? As described above, the hair cells of the canals make excitatory synapses onto vestibular sensory neurons. The cell bodies of these neurons are located just outside the labyrinth, in the **vestibular ganglion**. In animals that have a cochlea, the axons exiting the vestibular ganglion join with those of the cochlear neurons and enter the brain as the **eighth cranial nerve** (nerve VIII; often termed the auditory nerve, but more correctly called the vestibulocochlear nerve). The incoming axons from the vestibular ganglion terminate in the **vestibular nuclei** of the brainstem. As described in chapter 11, the vestibular nuclei give rise to the vestibulospinal tract and also represent an important source of sensory input for the cerebellum. These nuclei are located under the cerebellum, slightly posterior to the position where it balloons out from the upper surface of the brainstem (Fig. 12.8).

The vestibular nuclei contain several different types of neurons concerned with eye movements. These neurons are distinguished on the basis of the semicircular canal from which they receive inputs and the ocular motor neuron pool to which they project. Each canal produces eye movements in its own plane. For instance, stimulation of the horizontal semicircular canal produces horizontal eye movements, while vertical movements result from stimulation of the vertically oriented canals. Thus, the neurons in the vestibular nuclei that receive inputs from the horizontal canal must project to the motor neurons of the medial and lateral rectus muscles. Figure 12.9 summarizes this set of connections for the horizontal canal. The motor neurons of the medial rectus muscle for each eye are located in the ipsilateral oculomotor nucleus, while the motor neurons for each lateral rectus muscle are found in the ipsilateral abducens nucleus. The vestibular ganglion neurons make excitatory synapses on the interneurons of the vestibular nuclei. Some of these interneurons then project to the ipsilateral oculomotor nucleus, where they make excitatory synapses onto the motor neurons of the ipsilateral medial rectus muscle. Other vestibular nucleus interneurons send axons that cross the midline and make excitatory synapses onto the lateral rectus motor neurons in the contralateral abducens nucleus.

In addition to the excitatory interneurons, the vestibular nuclei contain inhibitory interneurons. For the horizontal semicircular canal, these inhibitory interneurons project to the ipsilateral abducens nucleus and to the contralateral oculomotor nucleus. (The connection from the inhibitory interneuron to the motor neurons is probably indirect for the medial rectus muscle, but it is shown as direct in Figure 12.9 for the sake of simplicity.) Thus, excitation of this subset of vestibular ganglion neurons rapidly inhibits the ipsilateral lateral rectus motor neurons and the contralateral medial rectus motor neurons.

Figure 12.9 illustrates the action of the synaptic connections described above that result when the head is rotated to the left, which causes the endolymph of the horizontal canals to flow in the opposite direction. For the canal on the left side of the head, the endolymph will flow toward the ampulla, depolarizing the hair cells and increasing the rate of action potentials in the vestibular-ganglion neurons on the left side. The increased excitation will be passed along to the interneurons of the vestibular nuclei. The interneurons will excite the motor neurons of the right-eye lateral rectus muscle and the left-eye medial rectus muscle. Both eyes will rotate to the

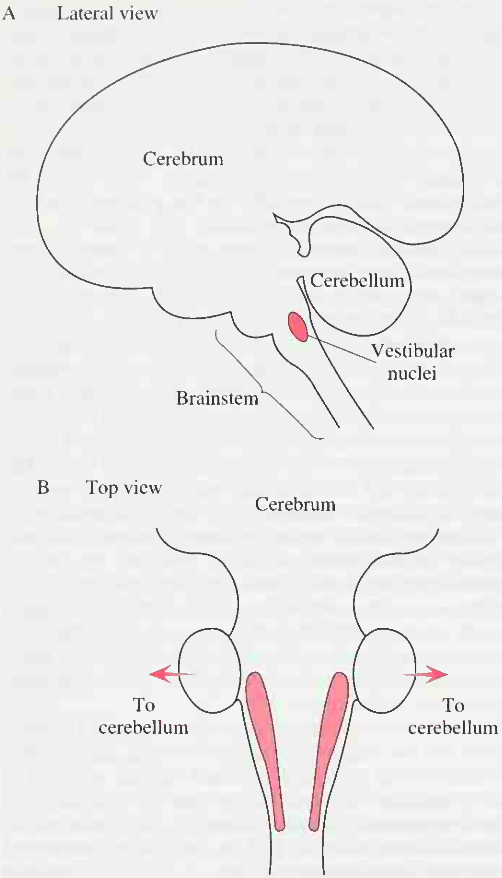
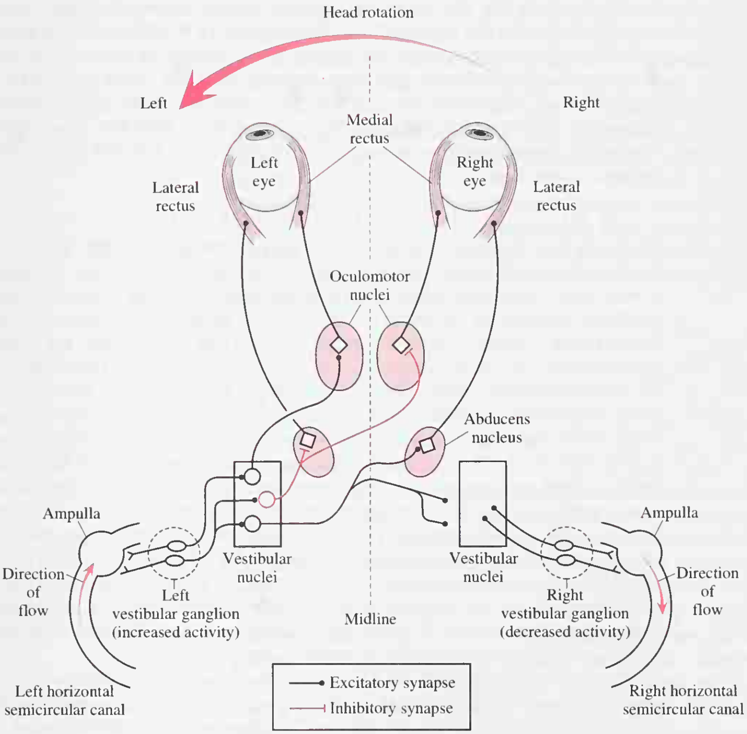


Figure 12.8
The location of the vestibular nuclei within the brainstem. (A) Lateral view. (B) Top view.

right, in the direction opposite to the head rotation. At the same time, the motor neurons of the left-eye lateral rectus muscle and the right-eye medial rectus muscle will be inhibited. This will reduce the tension in the muscles that oppose the rotation of the eyes to the right. The diagram in Figure 12.9 shows only the connections for the left horizontal semicircular canal. The right-side canal makes the same set of connections via the vestibular nuclei on the right side of the brainstem, producing a circuit that is the mirror image of that shown in the figure.

Figure 12.9
The circuitry of the vestibulo-ocular reflex. Head rotation to the left elicits eye movement to the right. Sensory information from the horizontal semicircular canal is distributed to the appropriate motor neurons by the interneurons of the vestibular nuclei. The cranial nerve nuclei are shown in pink; inhibitory neurons are red.



The endolymph flow induced in the right canal by head rotation to the left will move *away* from the ampulla, rather than toward the ampulla as on the left side. This movement hyperpolarizes the hair cells and *reduces* the rate of action potentials in the vestibular ganglion neurons of the right side. This reduced activity on the right side reinforces the actions of the *increased* activity of the left-side vestibular ganglion neurons. Excitation supplied by the interneurons of the right vestibular nuclei to the motor neurons of the left lateral rectus muscle decreases. At the same time, excitation to the motor neurons of the right medial rectus muscle is reduced, and inhibition to the right-eye lateral rectus motor neurons and the left-eye medial rectus motor neurons declines. A motor neuron of the lateral rectus muscle of the right eye, for example, will be doubly excited because of increased excitation from the excitatory interneurons of the vestibular nuclei on the left side of the brain and because of decreased inhibition coming from the vestibular nuclei on the right side of the brain.

Connections for the other semicircular canals follow the same basic scheme shown for the horizontal canals in Figure 12.9, although their exact patterns of projections depend on the required direction of the reflexive eye movements. The vestibular ganglion neurons for each canal project to a specific subset of interneurons within the vestibular nuclei, and these interneurons then provide the appropriate connections with the motor neurons in the three cranial nerve nuclei (nerves III, IV, and VI) that control the extraocular muscles.

The vestibulo-ocular reflex lacks feedback control

There are two striking features of the reflex pathway that leads from the semicircular canals to the motor neurons of the eye muscles. First, the path is very short, requiring only two synapses to reach from the neurons of the vestibular ganglion in the inner ear to the motor neurons at the output stage of the reflex (a third synapse is formed between the hair cell and the input process of the vestibular ganglion neurons, in the periphery). In this sense, the vestibulo-ocular reflex is reminiscent of the stretch reflexes we encountered in previous chapters. This short pathway gives the vestibulo-ocular reflex a very fast response latency: the conduction delay to the motor neurons is only about 15 thousandths of a second after the vestibular hair cells detect a head movement. This rapid response allows you to hold the visual world steady during the fast, vibratory head movements that occur, for instance, when your heel strikes the ground as you walk. This high speed is one reason that the nervous system uses vestibular information—rather than visual information—to stabilize the eye position. In a sense, monitoring head movement allows the nervous system to anticipate blurring of the image before it actually occurs. If visual information were used instead, then the blur would have to occur before it could be detected.

The second striking feature of the vestibulo-ocular reflex is the absence of feedback control in the pathway. In this regard, the VOR differs dramatically from the stretch reflexes. As we discussed in chapter 10, the stretch reflex is inherently a feedback mechanism. Input to the stretch reflex (passive stretch of the intrafusal muscle fibers) produces a motor output that reduces or cancels out the input, until the length set point is restored. The circuit shown in Figure 12.9, however, lacks any feedback about the success of the eye movements. This type of reflex is called an **open loop reflex** to indicate the lack of feedback that would complete the loop between output and input. By contrast, reflexes with feedback (like the stretch reflex) are termed **closed loop reflexes.** The success of the VOR depends on the precision of the excitatory and inhibitory synapses onto the motor neurons and interneurons, with exactly the right amount of eye movement necessary to balance a given amount of head rotation.

Although the VOR pathway shown in Figure 12.9 does not include direct sensory feedback, the reflex may still be altered. To ensure that eye movements produced by the VOR match head rotation correctly, the nervous system continually monitors VOR performance and modifies the strength of the excitatory and inhibitory connections to maximize stability of the visual world. The fast, direct path from the vestibular nucleus to the motor neurons may not appear to contain much room for modification. Nevertheless, the motor signals in this path are constantly compared with both vestibular and visual information, and additional signals are added at the vestibular nuclei and the motor neurons to fine-tune the accuracy of performance. If the movements of the eyes become smaller or larger than required to balance head movement, an error signal will be generated; this signal will then add to or be subtracted from the vestibular signal, compensating for the mismatch.

In chapter 11, we saw that the cerebellum modulates motor commands based on performance. Not surprisingly, then, the cerebellum plays an important role in this modification of the VOR based on experience. We will learn more about VOR modifiability when we discuss plasticity in the nervous system in chapter 21.

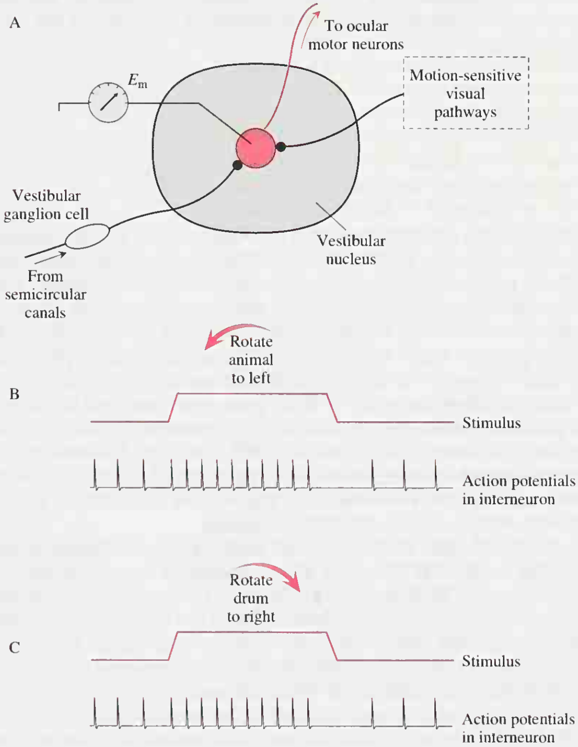
REFLEXIVE EYE MOVEMENTS: OPTOKINETIC REFLEX

In the vestibulo-ocular reflex, the reflexive movement of the eyes is triggered by head movement—not by movement of the visual image on the retina. The goal of the VOR is to maintain a constant retinal position for the image. The **optokinetic reflex** (OKR) also tends to maintain a constant image position on the retina. Unlike the VOR, it is triggered by motion of the external world, with the head position fixed. Most of us have experienced this type of eye movement while riding in a car or train. If we look out the side window while passing a series of telephone poles or fence posts, our eyes tend to track a single pole until the eyes reach their horizontal limit within the orbit. A rapid resetting movement then occurs in the opposite direction, followed by resumption of the slower tracking movement. This type of eye motion, with slower steady movement in one direction followed by rapid return movement in the opposite direction, is called **nystagmus**.

The usual experimental arrangement for eliciting the optokinetic reflex involves placing a subject at the center of a large rotating drum with vertical stripes. If the subject is rotated while the drum is held steady, it elicits the vestibulo-ocular reflex. If the drum is rotated while the subject is stationary, it elicits the optokinetic reflex. This type of reflex (also called the visual following response) can be observed in virtually all animals that have eyes.

Where does the visual information about movement enter the pathway controlling eye movements? The same groups of interneurons in the vestibular nuclei that are excited by inputs from the semicircular canals also receive inputs from the visual system and can be excited by moving visual stimuli. Figure 12.10 illustrates these effects of vestibular and visual stimulation on the firing of action potentials in the vestibular nucleus. If the neuron is excited when the animal is rotated to the left (see Fig. 12.10B), then the same neuron will also be excited when the animal remains stationary and the drum rotates to the right (see Fig. 12.10C). In both cases, the stimulus acts to

Figure 12.10
The optokinetic reflex and the vestibulo-ocular reflex act on the same set of interneurons in the vestibular nuclei. In this experiment, an animal is placed on a rotating stool in the center of a rotating drum. (A) A schematic diagram of the recording arrangement and the synaptic connections. (B) Rotating the head to the left increases the firing of action potentials in the interneuron. (C) Rotating the drum in the opposite direction also increases the firing of action potentials in the interneuron.



move the eyes toward the right in the orbit, compensating for the head movement in the one case and following the moving stimulus in the other. If the directions of rotation were reversed (that is, if the animal were rotated to the right or the drum were rotated to the left), the neuron of Figure 12.10 would be inhibited by both stimuli, and the rate of firing action potentials would decline during the stimulus.

Because they respond to visual stimuli, the interneurons of the vestibular nuclei could be regarded as part of a visual pathway as well as the vestibular pathway. This fact represents an essential feature of sensorimotor integration: information from more than one sensory system is combined to produce appropriate motor output. In the oculomotor system, the integration of different types of sensory information occurs in a particularly clear way and at a particularly low level in the motor pathway—only one synapse away from the motor neurons of the extraocular muscles. The rapid and low-level combination of vestibular and visual information makes functional sense as well, because under normal conditions we make both head and eye movements as we follow objects. Thus, accurate eye movements to follow moving stimuli require information about head motion.

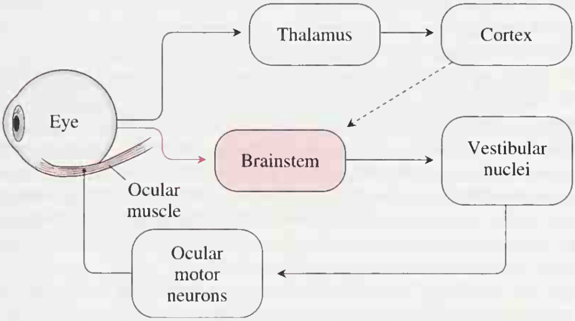
Although the vestibular nuclei received their name from their roles as recipients of the inputs from the vestibular apparatus, these nuclei can also be regarded as part of a more general machine that computes the excitation and inhibition of the various oculomotor neurons required to produce particular eye movements. The nervous system can reuse this computational machine for other systems that influence eye movements, without having to recreate and recalibrate the synaptic machinery controlling the motor neurons. In addition, by tapping into this machinery, other parts of the nervous system can access the supervisory circuitry in the cerebellum that generates error signals, which are used to ensure that eye movements produce the desired result.

The accessory optic system

What is the source of the visual information about movement? Visual information leaves the eye via the optic nerve and is passed via the thalamus to regions of the cerebral cortex that decipher the signals. These pathways and the information processing they perform are discussed in detail in chapter 17. In addition to this thalamic/cortical path, projections of the optic nerve bypass the thalamus and connect directly with brainstem neurons, forming a non-cortical path called the **accessory optic system** (Fig. 12.11). The brainstem neurons in this system are excited by moving visual stimuli. The visual projection to the brainstem likely represents a phylogenetically more primitive system for movement detection, used in the reflexive control of eye position. The neurons of the accessory optic system in turn send axons to the vestibular nuclei on both sides of the brain, where they make synaptic connections with the interneurons of the vestibular nuclei.

In many species, the accessory optic system is the principal source of visual motion information for eye movement control. In animals with a more developed cerebral cortex, such as primates, cortical areas also pass along information about moving visual stimuli to the oculomotor system in

Figure 12.11
A diagram of visual system inputs to the oculomotor systems in the brainstem. The accessory optic system is shown in red. The retina projects to the thalamus and to the brainstem; the brainstem also receives indirect projections from the visual portions of the cerebral cortex (dashed line).



the brainstem (indicated by the dashed line from the cortical visual areas to the brainstem in Figure 12.11). In addition to providing signals used in the optokinetic reflex, the cortical visual centers are important in generating other types of eye movements, as we will discuss in the next section.

VOLUNTARY EYE MOVEMENTS: SACCADES

As you read the words of this sentence, your eyes scan the page in a series of rapid jumps, fixating first on one group of words and then making a rapid lateral movement to fixate on the next group of words. These rapid jumps, called **saccades**, are the eye movements most commonly used by humans and other primates to scan the visual world. Eye movement during a saccade is extremely rapid. A small saccade (for example, a shift of approximately 10° in the angle of the eyes with respect to the head) is completed in 50 ms or less, and even a large saccade (approximately 30°) requires only about 100 ms.

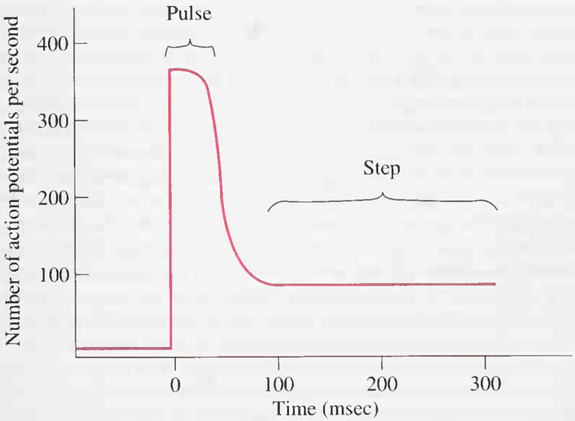
Saccades bring different portions of the visual environment into the center of the visual field, so that light coming from objects of interest falls on the **fovea** of the retina, where visual acuity is highest (chapter 16). Saccades are also found in animals that do not have a fovea. The neural machinery that produces the rapid movement most likely evolved first as a component of reflex systems, acting as a reset mechanism to return the eyes to central position in the orbit rapidly. For example, saccades are a normal component of the optokinetic nystagmus, producing the rapid phase of movement in the opposite direction after slow drift has moved the eyes to their extreme horizontal positions within the orbits. Later in evolution, the basic machinery of the saccade came under the control of higher centers involved in voluntary control of eye movements, allowing different visual targets to be brought to the fovea.

The saccade generator

In keeping with the idea that the saccade circuit is an old evolutionary development, the neurons that form the components of this circuitry are found within the brainstem reticular formation, in various nuclei stretching from the pons up to the midbrain. The output of the circuit is mediated via the final common path for control of the extraocular muscles—that is, the ocular motor neurons.

If we record the action potentials of an ocular motor neuron during a saccade, we would observe a firing pattern like that shown in Figure 12.12. At the onset of the saccade, the motor neuron fires a burst of action potentials at a very high rate, approaching 400 action potentials per second. This initial burst of activity, called the pulse phase, produces a strong and rapid contraction of the muscle. Rapidly overcoming the inertia of the eyeball and its supporting tissues, this contraction pulls the eye quickly into a new position within the orbit. The pulse phase lasts only 100 ms or less and

Figure 12.12
The pattern of action potentials in a motor neuron of an extraocular muscle during a saccade. The saccade is triggered at time 0 on the time axis. Initially, the motor neuron fires a burst of action potentials at a high rate (pulse phase). This high rate is maintained for a short time, followed by a decline to a lower rate (step phase).



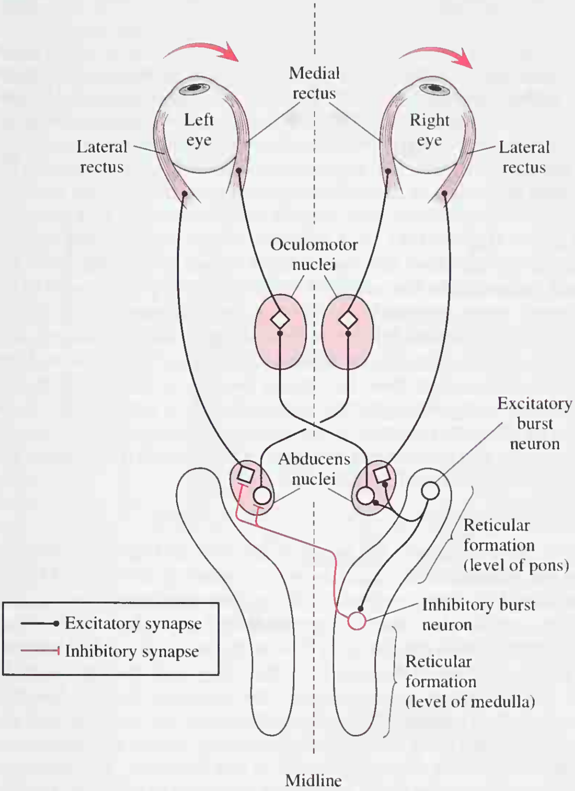
rapidly dies out as the eyeball approaches its new position. The rate of action potentials in the motor neurons does not decline to zero, however. Instead, the pulse phase is followed by a sustained plateau of activity at a moderate rate, called the step phase. It holds the eye steady at its new position and prevents relaxation caused by the elastic properties of the supporting tissues of the eyeball.

What neuronal connections account for the initial pulse phase of activity in the ocular motor neurons? The basic organization is summarized in Figure 12.13. As in our previous examples, we will consider the circuit only for a horizontal movement, which involves the medial and lateral rectus muscles. Note, however, that an equivalent set of neurons exists for vertical saccades. The diagram in Figure 12.13 shows only the circuitry for a saccade toward the right, which is controlled by interneurons located in the right side of the brain. On the left side, a mirror-image circuit drives saccades toward the left in the horizontal plane.

The trigger neuron for the burst phase is a type of interneuron called the **excitatory burst neuron**, which is located in a nucleus embedded within the reticular formation in the pons. Excitatory burst neurons fire a rapid burst of action potentials just before the onset of a saccade, and make a strong excitatory connection directly onto motor neurons of lateral rectus muscle of the right eye, in the abducens nucleus (cranial nerve VI) on the same side of the brain. This connection triggers the burst phase of action potentials in the lateral rectus motor neurons. In addition, the excitatory burst neurons make excitatory synapses with interneurons within the abducens nucleus that project to the contralateral nucleus of the oculomotor nerve (cranial nerve III). There, the interneurons make excitatory connections onto the motor neurons of the medial rectus muscle of the left eye, triggering their pulse phase. Through this set of connections (see Fig. 12.13), the excitatory burst neurons trigger a strong contraction of the left-eye medial rectus muscle and the right-eye lateral rectus muscle.

The excitatory burst neurons also send collateral branches of their axons to more posterior parts of the reticular formation, where they make excitatory synapses with another class of interneurons involved in the control of saccades, the **inhibitory burst neurons** (see Fig. 12.13). The input from the excitatory burst neurons triggers a burst of action potentials in these inhibitory interneurons just before the onset of the saccade. The axons of the inhibitory burst neurons cross the midline and synapse with the lateral rectus motor neurons of the contralateral abducens nucleus. This strong inhibitory input silences the motor neurons of the antagonistic horizontal muscle of the left eye, preventing it from opposing the strong pull produced by the contraction of the medial rectus muscle on that side. The inhibitory burst neurons also inhibit interneurons of the left-side abducens nucleus that provide excitatory inputs to the medial rectus motor neurons of the right-side oculomotor nucleus. Silencing the excitatory input to these motor neurons also reduces the tension in the medial rectus muscle of the right eye, so that it does not oppose the desired movement. An equivalent set of excitatory and inhibitory burst neurons is found on the left side of the brain; these neurons produce the pulse phase of saccades toward the left. Thus, stimulation of the excitatory burst

Figure 12.13
A schematic diagram of the basic circuitry for generating a saccade to the right. The cranial nerve nuclei are shown in pink; the inhibitory burst neurons are red.



neurons on a particular side of the brain will produce a saccade toward that side of the brain.

What generates the step phase of the motor neuron activity during a saccade? As we have seen, the burst of action potentials produced by the excitatory burst neurons triggers the rapid phase of the eye movement. For a large-amplitude saccade, the required strength and duration of muscle contraction are greater than for a smaller saccade. The pulse phase of action potential firing must also be larger and longer for a larger saccade. A larger saccade requires a higher rate of firing during the step phase, because a larger movement must overcome a greater passive resistance from the supportive tissues and antagonistic muscles. In other words, whenever the pulse phase is greater, the step phase is greater. Figure 12.14A shows examples of the time-course of activity in ocular motor neurons during large and small saccades.

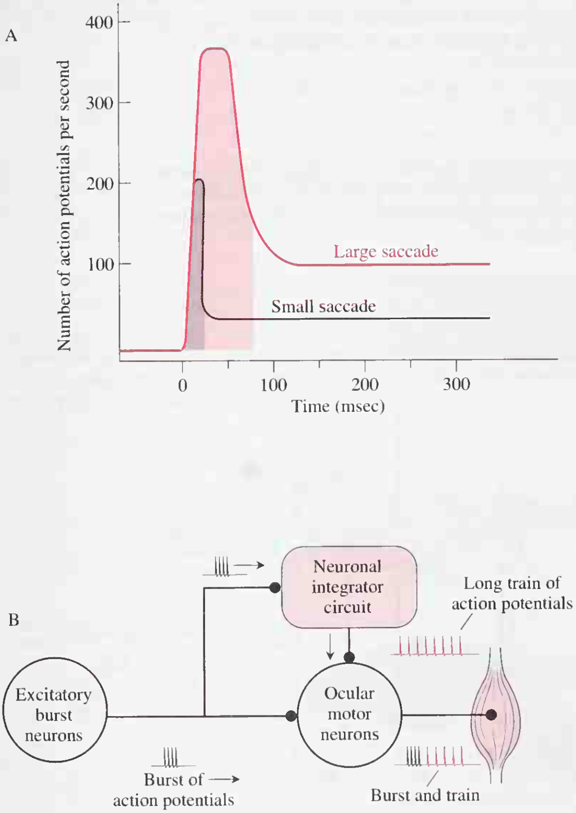
A simple way for the nervous system to monitor the size of the pulse phase is to sum (or integrate) the number of action potentials that occur during the high-frequency activity of the pulse phase. In Figure 12.14A, the gray area shows the integral of activity during the pulse phase for the small saccade, while the pink area shows the much greater integral during the pulse phase for the larger saccade. The signal that produces the pulse phase is the burst of action potentials in the excitatory burst neurons, and the axons of these neurons send collaterals that provide excitatory input to a neuronal integrator circuit (Fig. 12.14B). This neuronal circuit converts the burst of input action potentials into a sustained train of output action potentials. The rate of action potentials in the output of the integrator is proportional to the total number of action potentials produced in the excitatory burst neurons. The neurons of the neuronal integrator then make excitatory synapses onto the same ocular motor neurons that receive inputs from the excitatory burst neurons. Thus, the output from the motor neuron to the ocular muscle contains both the rapid burst and the sustained train of activity. This is the desired pattern. The exact identity of the integrator circuit neurons remains unknown, as does the mechanism by which they convert a burst of input action potentials into a sustained output.

Control of the saccade generator: pause neurons

Now that we have discussed the types of neurons and their connections underlying the generation of a saccade, we can move up the control hierarchy to consider the neural systems that regulate the lower-level saccade generator. The next level of control is provided by a general-purpose saccade inhibition system, which consists of a class of interneurons, called **omnidirectional pause neurons**, that are found within the **raphe nucleus** along the midline of the brainstem at the level of the abducens nerves. Electrical recordings show that omnidirectional pause neurons fire continuously at a steady rate, except just prior to and during a saccade (hence the name *pause neuron*). They cease firing during a saccade in any direction, without directional specificity (hence the name *omnidirectional* pause neuron). By sending axons to the excitatory burst neurons, omnidirectional pause neurons provide a sustained inhibition that keeps the burst neurons from firing, except during creation of a saccade.

Thus, the release from inhibition by the omnidirectional pause neurons is one of the triggers for activating the saccade generator. If the raphe nucleus is stimulated electrically, thereby artificially activating the omnidirectional pause neurons, animals are unable to produce saccades, although eye movements produced by the vestibulo-ocular system remain unaffected. If the omnidirectional pause neurons are stimulated artificially during the

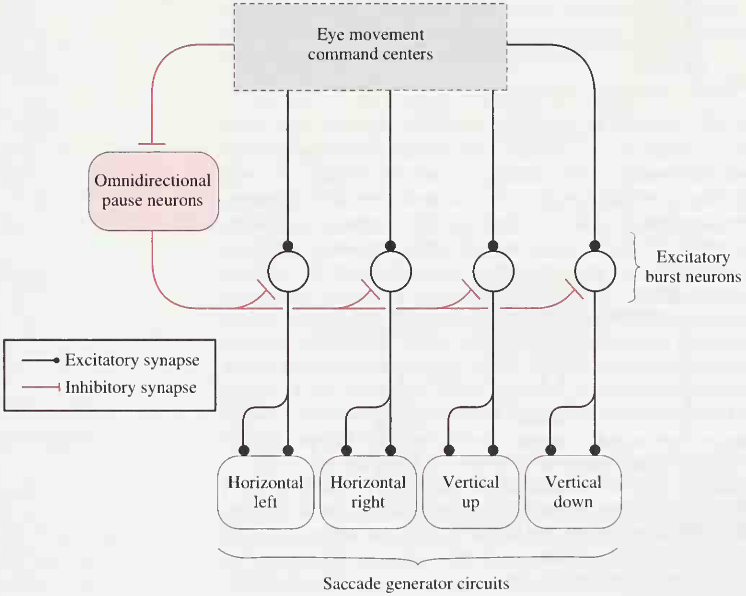
Figure 12.14
The circuitry for generating pulse and step phases of ocular motor neuron activity during a saccade. (A) The time-course of pulse and step phases during large and small saccades. The large saccade is shown in red; the small saccade in black. The area of the pulse phase is indicated in gray for the small saccade and in pink for the large saccade. (B) The neuronal connections for generating the step phase by integrating the activity during the burst of firing by the excitatory burst interneurons. The action potentials from the integrator circuit are shown in red, as are the action potentials in the ocular motor neuron that originate from the excitatory input from the integrator neurons.


A
400
300
200
100
Number of action potentials per second
Large saccade
Small saccade
0
100
200
300
Time (msec)
B
Neuronal integrator circuit
Long train of action potentials
Excitatory burst neurons
Ocular motor neurons
Burst of → action potentials
Burst and train

performance of a saccade, the saccade terminates prematurely. Thus, the cessation of activity in the omnidirectional pause neurons is obligatory for triggering a saccade.

In addition to the inhibitory input from the omnidirectional pause neurons, the excitatory burst neurons receive inputs descending from higher motor control centers that are involved in the planning and programming of saccades. These descending commands excite the burst neurons but inhibit the pause neurons; the combination of these actions then activates the burst neurons and initiates the saccade. The omnidirectional pause neurons act as an overall gate, permitting the saccade to be activated by the descending excitatory command. The selection among the various possible saccade directions is then determined by the identity of the saccade circuits activated by descending motor commands and the strength with which they are stimulated. This situation is depicted in Figure 12.15.

Figure 12.15
A schematic diagram for the connections of the saccade command centers (gray) with the excitatory burst neurons responsible for the four saccade directions. The omnidirectional pause neurons (red) make inhibitory connections on all of the excitatory burst neurons. The higher centers also inhibit the pause neurons (red connection).

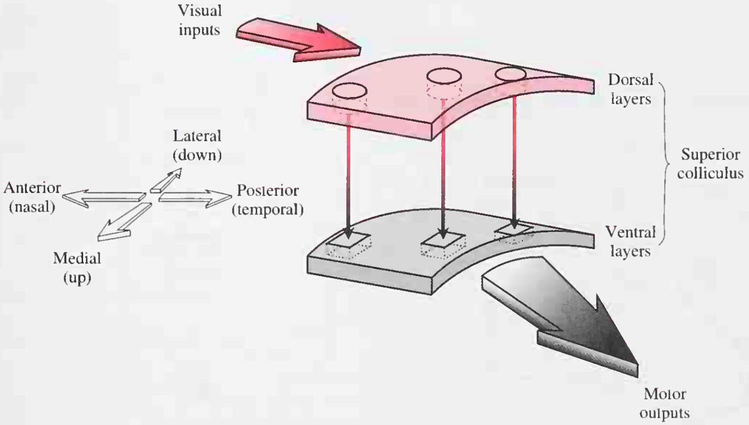


Control of the saccade generator: the superior colliculus

One of the principal sources for the descending motor commands shown in Figure 12.15 is the superior colliculus, which is found on the top surface of the brainstem (see Fig. 12.3). The neurons in this region of the brain receive extensive inputs from the visual system and send axons to the areas of the brainstem where excitatory burst neurons are found. The superior colliculus is organized into several layers. The dorsal layers (near the surface of the brainstem) receive visual inputs, including direct input from the retina. The ventral layers (deeper within the brainstem) provide the superior colliculus's output, including the descending axons that connect with the oculomotor systems in the reticular formation. This arrangement is shown in Figure 12.16.

Both the dorsal layers and the ventral layers are organized into two-dimensional maps: a sensory map of the visual fields in the dorsal region, and a motor map of relative eye position in the ventral region. For example, a visual stimulus appearing in the upper part of the visual field would excite neurons in the medial portion of the dorsal layers of the superior colliculus. Similarly, electrical stimulation of the medial portion of the ventral layers would elicit a saccade upward. Thus, electrical stimulation in the ventral layers produces eye movement toward the point in the visual field represented by the corresponding, overlying portion of the dorsal layers. The direction and magnitude of the eye movement are independent (within the

Figure 12.16
A schematic diagram of the layers of the superior colliculus. Visual inputs arrive in the dorsal layers (red) and are relayed to the output layers (gray). The three-dimensional orientation is indicated by the compass arrows.



limits of the possible range of motion) of the absolute eye position within the orbit. Thus, there is a topographical correspondence between the maps in the ventral and dorsal layers.

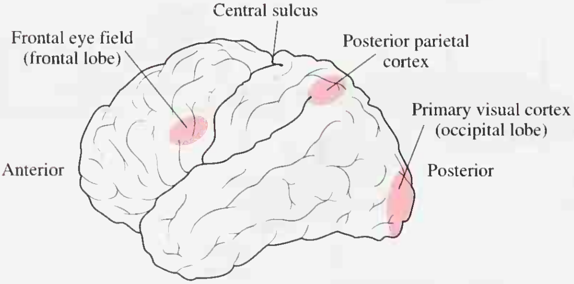
These observations suggest that the superior colliculus translates a sensory map of the external world (projected onto the neurons of the dorsal layers) into a set of motor commands that move the eyes so that the fovea is centered at that position (commands produced by the ventral layers). This translation process is indicated by the arrows connecting the two layers in Figure 12.16. Unfortunately, neurobiologists do not understand exactly how this translation process is carried out by the synaptic interactions among the layers of the superior colliculus. Nevertheless, this remapping of the *x, y* coordinates of the visual world into the *x, y* coordinates of the saccade generators is exactly what we mean by sensorimotor integration in the nervous system. Interestingly, some neurons in the superior colliculus respond to both auditory and visual stimulation, suggesting that they might be important for generating eye movements toward external targets that are heard, as well as those detected visually.

Control of the saccade generator: cortical eye movement centers

The superior colliculus is of great importance in the programming of saccades, but cortical regions are also important, particularly in primates. The cervical regions include parts of the frontal lobes and the parietal lobes, which are shown in Figure 12.17.

One of the major areas involved in saccades in the cortex is the **frontal eye field**, which is located bilaterally in the frontal cortex (in part of Brodmann's area 8), just in front of the primary motor cortex. The frontal eye fields contain neurons that fire action potentials prior to saccades. These neurons send connections to the superior colliculus, as well as directly to the oculomotor system in the reticular formation. The frontal eye fields also send

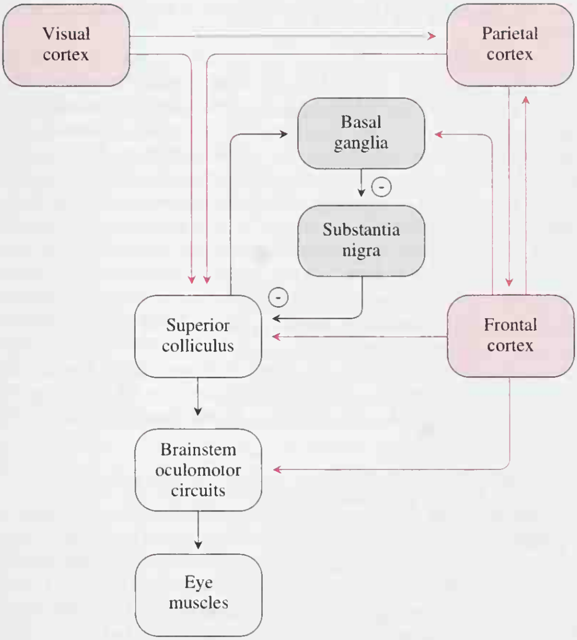
Figure 12.17
The approximate locations of the cortical areas that affect eye movements.


Central sulcus
Frontal eye field (frontal lobe)
Posterior parietal cortex
Primary visual cortex (occipital lobe)
Anterior
Posterior

outputs to the basal ganglia. The interconnections of the cortical and subcortical eye-movement systems are summarized in Figure 12.18.

When electrical stimulation is applied to the frontal eye field on one side of the brain, a saccade of both eyes is elicited toward the opposite side (for example, stimulation of the left frontal eye field causes the eyes to move to the right). The latency associated with this response is short (less than 0.1 s), suggesting that the neurons of the frontal eye fields are closely connected to the saccade generator circuitry. The direct projections from the frontal eye fields to the superior colliculus and the brainstem reticular formation are consistent with a close relationship between the frontal cortex and the motor output during saccades. The frontal eye fields are thought to issue the command that initiates a saccade. Electrical recordings of action potential activity demonstrate that individual neurons within the frontal eye fields increase their activity just before the onset of a saccade. Activation of a particular neuron is associated with the occurrence of a saccade in a

Figure 12.18
The connections among the cortical eye-movement areas (red) and subcortical systems. The minus signs indicate inhibitory connections.



particular direction. Thus, the cells of the frontal eye fields appear to code the desired direction of a saccade, based on which group of cells becomes active. This active group of cells stimulates the appropriate saccade generators in the brainstem, both by direct projections and by influencing the activity of the superior colliculus.

The frontal eye fields receive input from another cortical region involved in the eye movements—the **posterior parietal cortex** (see Fig. 12.17). Although electrical stimulation in this part of the cortex can elicit saccades, the latency period is longer and more variable than when stimulation is applied directly to the frontal eye fields. The parietal cortex is thought to carry out higher-level integration of sensorimotor information related to the planning of eye movements, including the selection of visually detected objects to which saccades will be directed (visual attention). Of particular interest is a portion of the parietal cortex buried within the folds of one of the deep sulci of the region. This region, called the **lateral intraparietal area**, contains neurons that fire action potentials in response to visual stimuli and in association with the production of saccades. The axons of neurons in the lateral intraparietal area project to both the superior colliculus and the frontal eye fields. Like the superior colliculus, the lateral intraparietal area appears to connect sensory information with motor outputs, specifically those related to voluntary saccades. Individual neurons within the lateral intraparietal area increase their activity for saccades of a particular direction and amplitude.

Unlike in the superior colliculus, the activity of neurons in the lateral intraparietal area is not closely tied to the immediate production of saccades. In fact, some neurons in the lateral intraparietal area, called **intended-movement neurons**, seem to code for the intention to make a saccade of a particular size and direction, rather than the actual triggering of the saccade. This neuronal behavior was revealed through experiments that required trained monkeys to make a delayed saccade to the *remembered* location of a target. In this task, an animal must look at a central fixation point while a visual target is briefly flashed in the periphery of the visual field. At some later time, the animal must make a saccade to the remembered position of the target, which is no longer present. The intended-movement neurons that code for saccades in the appropriate direction begin firing shortly after the target stimulus appears, and they continue to fire action potentials throughout the delay period (even though the target is absent) until the saccade actually occurs. These interesting neurons thus seem to be signaling the intention to make the saccade, supporting a motor-planning role for the lateral intraparietal area.

Control of the saccade generator: the role of the basal ganglia

In chapter 11, we discussed the role of the basal ganglia and the substantia nigra in the coordination and initiation of locomotion. These brain motor control centers also influence the eye movement systems described in this chapter. The superior colliculus, for example, receives important input from part of the substantia nigra. This connection seems to be required for the inhibition of saccades (indicated by the minus sign next to the connection in Figure 12.18).

The inhibitory input from the substantia nigra acts as a brake to prevent saccades until they are ordered by the cortical centers. To release the brake and initiate a saccade, an inhibitory input from the basal ganglia to the substantia nigra is activated. The saccade command descends from the frontal eye fields to the superior colliculus and to the caudate nucleus of the basal ganglia, which contains neurons that make the inhibitory synaptic connections with the substantia nigra. In this way, the superior colliculus is activated both by direct excitatory command and by the indirect removal of the inhibitory influence from the substantia nigra (inhibiting the inhibitor).

SUMMARY

In this chapter, we have explored some ways in which sensory information is translated into motor output, using examples from the mechanisms that control movement of the eyes. Sensory information is vital for the proper performance of the motor output systems at all levels in the hierarchy. Within the brainstem, reflex circuits rapidly translate vestibular signals originating in the semicircular canals into motor signals for the extraocular muscles, allowing eye movements to compensate quickly for movements of the head. The main goal of these reflex circuits is to maintain a stable image on the retina during locomotion.

Motion in the visual field can also trigger reflexive movements of the eyes, which match the speed of the moving object so that the image remains in a constant location on the retina. These reflexive movements consist of a slow movement in the same direction as the moving object, followed by a fast resetting movement in the opposite direction. The latter movement restores the eyes to a more centered position within the orbit.

Fast movements, called saccades, are also made voluntarily to bring various objects of interest within the visual field into the center of the field, where the image will fall on the fovea of the retina. Saccades are produced by neuronal circuits in the brainstem that operate in parallel with the pathways of the vestibular reflex system. The brainstem saccade generators are controlled by commands from the superior colliculus and from the frontal eye fields in the frontal lobes of the cerebral cortex. The superior colliculus receives sensory information from the visual system, which is used to construct a two-dimensional map of the visual fields. Translation of this map of visual space into a map of saccade space allows command neurons that trigger saccades of the proper direction and magnitude to be activated to bring the fovea to the desired position. In primates, a similar mapping of visual space into saccade space apparently occurs in parts of the parietal cortex as well.

The saccade circuits of the superior colliculus are inhibited by input from the substantia nigra. The frontal eye fields in the frontal cortex trigger saccades, both by activating the circuits in the superior colliculus and by activating neurons in the caudate nucleus that in turn inhibit the inhibitory neurons of the substantia nigra.

13

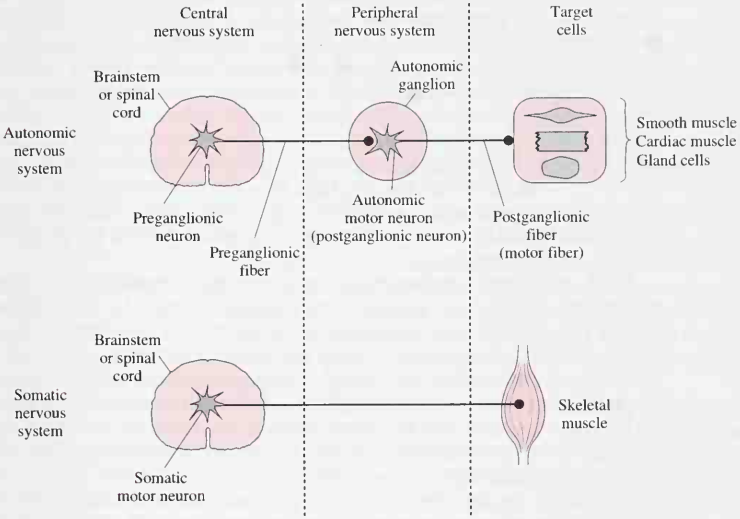
The Autonomic Nervous System

The motor functions we have described so far have been concerned with the control of skeletal muscles. These muscles produce overt movements of the body and give rise to the observable external actions that we normally consider to be the "behavior" of an animal. Even in an animal that might appear to be quiescent, however, the nervous system remains quite busy coordinating many other ongoing motor actions that do not involve skeletal muscles. These motor activities include regulation of digestion, maintenance of the proper glucose balance in the blood, regulation of heart rate, and so on. The part of the nervous system that controls these functions is called the **autonomic nervous system.** Its motor targets include gland cells, cardiac muscle cells, and smooth muscle cells such as those found in the gut. In contrast, the parts of the nervous system we have been discussing up to this point—whose motor targets are the skeletal muscles—are collectively called the **somatic nervous system.**

In addition to targeting different types of cells, the autonomic and somatic nervous systems differ in other ways. For example, in the somatic nervous system, the cell bodies of the motor neurons are located within the central nervous system, either in the spinal cord or in the nuclei of cranial nerves in the brainstem. By contrast, the cell bodies of the motor neurons in the autonomic nervous system are located outside the central nervous system altogether, in a system of **autonomic ganglia** distributed throughout the body. The central nervous system controls these autonomic ganglia via output neurons called **preganglionic neurons,** which are located in the spinal cord and brainstem. This arrangement is shown in Figure 13.1. The motor neurons in the autonomic ganglia are also called **postganglionic neurons.** The axons of the preganglionic neurons entering the ganglia are known as **preganglionic fibers,** and the axons of the autonomic motor neurons carrying the output to the target cells are called **postganglionic fibers.** Thus, in the somatic nervous system, the motor commands exiting from the central nervous system go directly to the target cells; in the autonomic nervous system, the motor commands from the central nervous system are relayed via an additional synaptic connection in the peripheral nervous system.

The autonomic and somatic nervous systems also differ in the effects that the motor neurons have on the target cells. Chapter 7 discussed in detail the synaptic interaction between motor neurons and skeletal muscle cells at the neuromuscular junction. All of the somatic motor neurons release acetylcholine as their neurotransmitter, and the effect on the skeletal muscle cells

Figure 13.1
Differences between autonomic and somatic nervous systems. (Top) In the autonomic nervous system, the motor neurons are located outside the central nervous system, in autonomic ganglia. The motor neurons contact smooth muscle cells, cardiac muscle cells, and gland cells. The central nervous system controls the ganglia via preganglionic neurons. (Bottom) In the somatic nervous system, the motor neurons are located within the central nervous system and contact skeletal muscle cells.



is always excitatory—that is, contraction is stimulated. In the autonomic nervous system, however, some motor neurons release acetylcholine while other motor neurons release the neurotransmitter norepinephrine (chapter 8). Furthermore, an autonomic motor neuron may either excite or inhibit its target cell. In general, if norepinephrine excites the target cells, then acetylcholine inhibits them; the reverse is also true. For example, norepinephrine increases the rate at which the heart beats, while acetylcholine decreases the heart rate.

The norepinephrine-releasing and acetylcholine-releasing motor neurons are organized into anatomically distinct divisions of the autonomic nervous system: the **sympathetic division** (norepinephrine-releasing) and the **parasympathetic division** (acetylcholine-releasing). Consequently, the ganglia containing the sympathetic motor neurons are called sympathetic ganglia, and those containing parasympathetic motor neurons are termed parasympathetic ganglia. Most of the sympathetic ganglia are arrayed parallel to the spinal column with one pair of ganglia for each vertebral segment. These

paravertebral ganglia are interconnected by thick, longitudinal bundles of axons that contain the preganglionic fibers exiting from the spinal cord. These connectives and the paravertebral ganglia form two long chains parallel to the spinal column, sometimes referred to as the **sympathetic chains.** In addition to the paravertebral ganglia, other sympathetic ganglia called the **prevertebral ganglia** are found within the abdomen.

The parasympathetic ganglia are distributed more diffusely throughout the body and tend to be located relatively close to their target organs. In some cases, the parasympathetic ganglia are actually located within the target organ itself—for example, in the heart. Because the sympathetic ganglia are located predominantly near the central nervous system and the parasympathetic ganglia are typically located near their target organs, the preganglionic fibers of the sympathetic nervous system are usually much shorter than the preganglionic fibers of the parasympathetic nervous system. To reach the postganglionic neurons, the parasympathetic preganglionic fibers must extend all the way from the central nervous system to the vicinity of the target organ. Conversely, the postganglionic fibers are typically much longer in the sympathetic nervous system than in the parasympathetic nervous system.

Most target organs receive inputs from both the sympathetic and parasympathetic divisions of the autonomic nervous system. As noted above, these inputs produce opposing effects on the target. In general, excitation of the sympathetic nervous system places the organism in "emergency mode," ready for vigorous activity. In contrast, the parasympathetic nervous system places the organism in a "vegetative mode." For example, sympathetic activity increases the heart rate and blood pressure, diverts blood flow from the skin and viscera to the skeletal muscles, and reduces intestinal motility—all preparations appropriate for rapid reaction to an external threat. Parasympathetic activity, on the other hand, decreases heart rate and blood pressure, and promotes blood circulation to the gut and intestinal motility. Such actions are appropriate for resting and digesting, in the absence of any threatening situation in the environment.

AUTONOMIC CONTROL OF THE HEART

To understand how the motor neurons of the sympathetic and parasympathetic divisions exert their actions on target cells, we will explore an example of autonomic action: the neural control of the heart. The heart consists of muscle cells, which are in some ways similar to the skeletal muscle cells we encountered in chapter 9. There are also some important differences, however, and we must understand these differences before we can examine the effects of sympathetic and parasympathetic inputs on the heart. First, we will discuss the electrical and mechanical properties of the heart muscle, before returning to the modulation of those properties by norepinephrine and acetylcholine.

The pattern of cardiac contraction

Cardiac muscle cells contain a contractile apparatus like that of other striated muscle, consisting of bundles of myofilaments with a microscopic structure like that described in chapter 9. Unlike other striated muscles, however, the heart muscle is specialized to produce a rhythmic and coordinated contraction that drives the blood efficiently through the blood vessels. The heart must accomplish a number of tasks if it is to carry out its role in providing oxygen to the cells of the body. It must receive the oxygen-poor blood returning from the body tissues via the venous circulation and send that blood to the lungs for oxygenation. It must also receive the oxygenated blood from the lungs and send it out through the arterial circulation to the rest of the body. Carrying out these tasks requires precise timing of the contractions of the various heart chambers. Otherwise, the flow of oxygenated blood will not occur efficiently or will cease altogether—with disastrous consequences. What is the normal timing sequence of the heart contractions underlying the coordinated pumping of the blood?

Figure 13.2 provides a schematic diagram of the flow of blood through a human heart during a single contraction cycle. Humans, like all other mammals, have a four-chambered heart, consisting of the left and right **atria** and the left and right **ventricles.** The two atria can be envisioned as the receiving chambers, or "priming" pumps, of the heart; the two ventricles represent the "power" pumps of the circulatory system. The right atrium receives the blood returning from the body through the veins, and the left atrium receives the freshly oxygenated blood from the lungs.

During the phase of the heartbeat when the atria are filling with blood, the valves connecting the atria with the ventricles remain closed, preventing flow of blood into the ventricles. When the atria become filled with blood, they contract. The subsequent increase in pressure opens the valves leading to the ventricles and drives the collected blood into the ventricles. At this point, the muscle of the ventricles is relaxed, and the valves connecting the ventricles to the vessels leaving the heart are closed. When the ventricles have filled with blood, they contract, opening these valves and delivering the power stroke to drive the blood out to the lungs and to the rest of the body (see Fig. 13.2B). Thus, during a normal heartbeat, the two atria contract together, followed (after a delay) by the simultaneous contraction of the two ventricles.

Coordination of contraction across cardiac muscle fibers

If the contraction of a heart chamber is to expel fluid, all of the individual muscle fibers making up the walls of that chamber must contract together. This unified contraction constricts the cavity of the chamber and propels the blood into the blood vessels of the circulation. In skeletal muscles, an action potential in one muscle fiber remains confined to that fiber and does not influence neighboring fibers; therefore, contraction is restricted to the particular fiber undergoing an action potential. In cardiac muscle, however, the situation is quite different. When an action potential is generated in a cardiac muscle fiber, it creates action potentials in the neighboring fibers, which in turn set up action potentials in their neighbors, and so on. Thus,

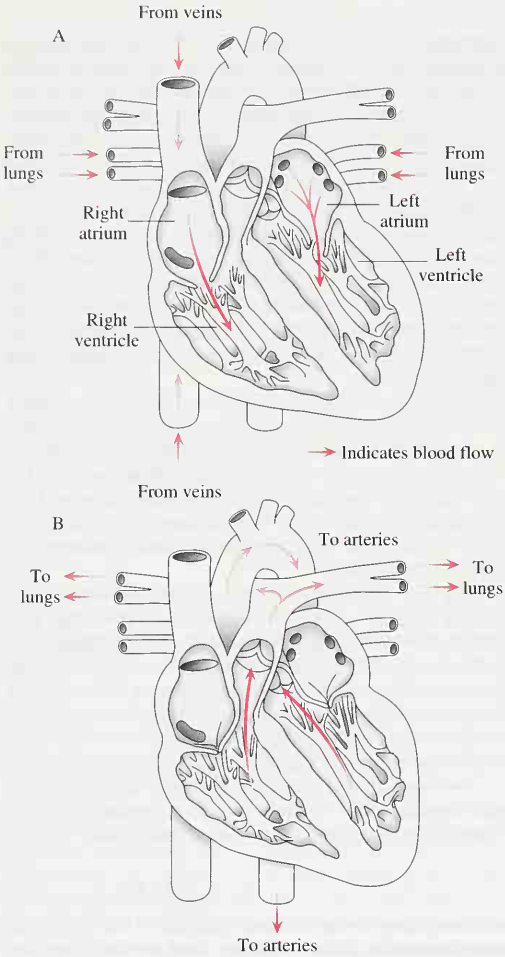
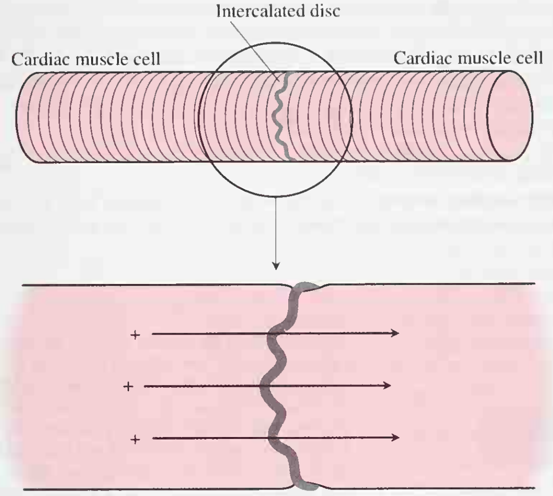


Figure 13.2
Schematic drawings of the state of the heart valves and the direction of blood flow during two stages in a single heartbeat. (A) The atria are contracting and the ventricles are filling with blood. (B) The valves between the atria and ventricles are closed and the ventricles are contracting, forcing the blood out to the lungs (right ventricle) and to the arteries leading to the rest of the body (left ventricle).

the excitation spreads rapidly through the muscle fibers of the chamber, thereby ensuring that all fibers contract together.

What characteristic of cardiac muscle fibers allows the action potential to spread from one fiber to another in this manner? Consider the microscopic structure of the cells of cardiac muscle (Fig. 13.3). At the ends of each cardiac cell, the plasma membranes of neighboring cells come into close contact at

Figure 13.3
Electrical current can flow from one cardiac muscle cell to another through specialized membrane junctions located in a region of contact called the intercalated disc.



specialized structures called **intercalated discs.** The contact at this point allows electrical current flowing inside one fiber to cross directly into the interior of the next fiber; in electrical terms, the neighboring cells can be considered to form one larger cell.

Recall from chapter 5 that an electrical current flowing along the interior of a fiber has at each point two paths from which to choose: across the plasma membrane or along the interior of the fiber. The amount of current taking each path at a particular point depends on the relative resistances of the two paths; the higher the resistance, the smaller the amount of current choosing that path. Normally, at the point where one cell ends and the next begins, current has little opportunity to flow from one cell to the other because it would have to flow out across one cell membrane and in across the other. This route represents a high-resistance path because the current must cross two membranes. At the specialized structure of the intercalated disc, however, the resistance to current flow across the two membranes is low, favoring the path to the interior of the neighboring cell. Thus, depolarizing current injected into one cell during an action potential can spread directly into neighboring cells, setting up an action potential in those cells as well. The low-resistance path from one cell to another travels through membrane structures called **gap junctions.** These structures consist of arrays of small pores directly connecting the interiors of the joined cells, permitting small molecules like ions to pass directly from one cell to another.

When electrical current can pass from one cell to another (as in cardiac muscle), those cells are said to be **electrically coupled.** An electrophysiological experiment to demonstrate this behavior is illustrated in Figure 13.4. When current is injected into a cell, no response occurs in a neighboring cell if the cells are not electrically coupled. If the two cells are coupled via gap junctions, however, both cells show a response to the injected current because the ions carrying the current inside the cell can pass directly through the gap junction. If the depolarization is large enough, it will trigger an action potential in both cells simultaneously.

Generation of rhythmic contractions

The electrical coupling among cardiac muscle fibers explains how contraction can occur synchronously in all fibers of a chamber. We will now consider

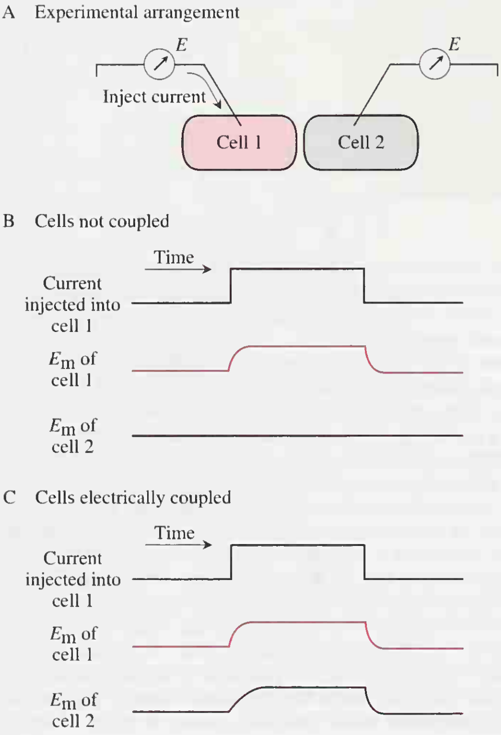


Figure 13.4
The results of an experiment in which the membrane potentials of two cells are measured simultaneously with intracellular microelectrodes. (A) A depolarizing current is injected into cell 1. (B) If the cells are not electrically coupled, the depolarization occurs only in the cell into which current was injected. (C) If the cells are electrically coupled via gap junctions, a depolarization occurs in both cell 1 and cell 2.

the control mechanisms responsible for the repetitive contractions that characterize the beating of the heart.

If a heart is removed from the body and placed in an appropriate artificial environment, it will continue to contract repetitively, even though it is isolated from the nervous system and the rest of the body. In contrast, a skeletal muscle isolated under similar conditions will not contract unless its nerve is activated. The rhythmic activity of the heart muscle is an inherent property of the individual muscle fibers making up the heart—another important difference between cardiac muscle fibers and skeletal muscle fibers. This difference can be demonstrated dramatically in experiments in which muscle tissue is dissociated into individual cells, which are placed in a dish isolated from one another and from the influence of any other cells (such as nerve cells). Under these conditions, muscle cells from skeletal muscles remain quiescent and do not contract in the absence of their neural input. Cells from cardiac muscle, however, continue to contract rhythmically even in isolation. Thus, rhythmic contractions of heart muscle are generated by built-in properties of the cardiac muscle cells.

Before we can examine the membrane mechanism underlying this autorhythmicity, we must understand the action potential of cardiac muscle cells. In keeping with the different behavior of cardiac cells, this action potential has characteristics that differ from those of action potentials of neurons or skeletal muscle cells.

The cardiac action potential

In chapters 5 and 6, we discussed the ionic mechanisms underlying the action potential of nerve membrane. The action potential of skeletal muscle fibers is fundamentally the same as that associated with neurons. The cardiac action potential, however, differs in several important ways. Figure 13.5 compares the characteristics of action potentials of skeletal and cardiac muscle cells.

One striking difference relates to the time scale: cardiac action potentials can last several hundred milliseconds, while skeletal muscle action potentials typically begin and end in 1 to 2 ms. A long-lasting action potential like the cardiac action potential can arise when voltage-dependent calcium channels contribute to the action potential (see chapter 5). Recall that these channels open upon depolarization and permit influx of positively charged calcium ions. This calcium influx produces a long-lasting plateau of depolarization during the action potential. In addition, the plateau of the cardiac action potential is associated with a reduction in the potassium permeability, caused by a type of potassium channel that remains open as long as the membrane potential is near its normal resting level and closes upon depolarization. This behavior is the reverse of that seen with the gated potassium channel of the nerve action potential. The reduction in potassium permeability caused by the closing of this channel tends to depolarize the cardiac muscle fiber. Both the opening of the calcium channels and the closing of the potassium channels contribute to the prolonged action potential in cardiac muscle cells.

The initial rising phase of the cardiac action potential is produced by voltage-dependent sodium channels very much like those found in the nerve

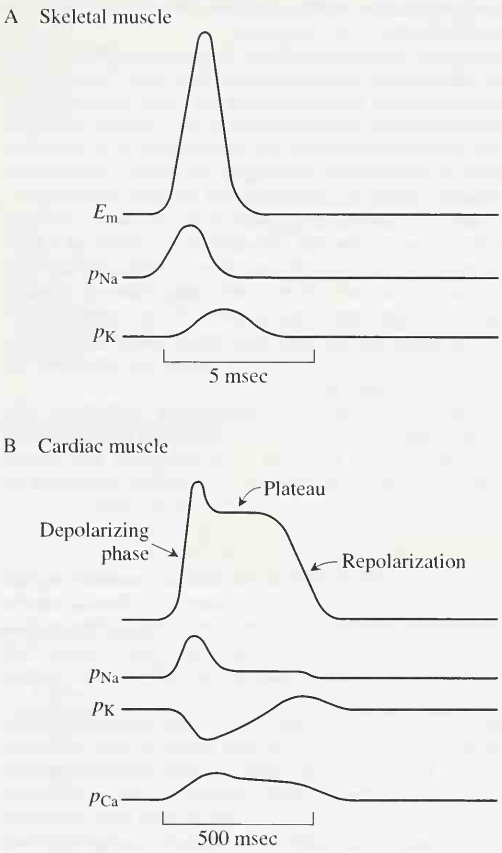


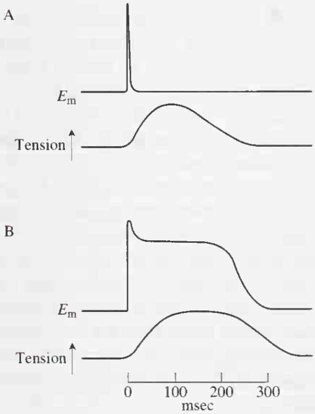
Figure 13.5
The sequence of permeability changes underlying the action potentials of (A) skeletal muscle fibers and (B) cardiac muscle fibers. Note how dramatically the time scales differ.

membrane. These channels drive the rapid initial depolarization and are responsible for the brief initial spike of the cardiac action potential before the plateau phase begins. Like the sodium channels of the neuronal membrane, they rapidly close (inactivate) with maintained depolarization. Unlike the nerve sodium channels, this inactivation is not total; a small increase in sodium permeability is maintained during the plateau.

How is the cardiac action potential terminated? First, the calcium permeability of the plasma membrane slowly declines during the maintained depolarization. This decline might be a consequence of the gradual build-up of internal calcium concentration as calcium ions enter the muscle fiber through the open calcium channels. Internal calcium ions are thought to act directly or indirectly on the calcium channels, causing them to close. Second, the potassium permeability of the plasma membrane increases, which drives the membrane potential toward the potassium equilibrium potential and repolarizes the muscle cell. Some evidence suggests that this increase in potassium permeability is partly due to voltage-sensitive potassium channels that open in response to the depolarization during the action potential (like the n gates of the nerve membrane). Calcium-activated potassium channels (see chapter 5) might also contribute to the delayed rise in potassium permeability.

One functional implication of the prolonged cardiac action potential is that the duration of the action potential controls the duration of the contraction in cardiac muscle. Figure 13.6 compares the action potential and contraction of cardiac muscle fibers with those of skeletal muscle fibers. In skeletal muscle, the action potential only triggers the contractile events; the duration of the contraction is controlled by the timing of calcium release and calcium reuptake by the sarcoplasmic reticulum, not by the duration of the action potential. In cardiac muscle fibers, however, only the initial part of the contraction is controlled by calcium from the sarcoplasmic reticulum; the contraction is maintained by the influx of calcium ions across the plasma membrane during the plateau phase of the cardiac action potential. For this reason, the duration of the contraction in the heart can be altered by changing the duration of the action potential in the cardiac muscle fibers. Thus, changing the action potential duration is an important mechanism for modulating the pumping action of the heart.

Figure 13.6
(A) In a skeletal muscle fiber, the action potential is much briefer than the resulting contraction. Thus, the action potential acts only as a trigger for the contraction, which proceeds independently of the duration of the action potential. (B) In a cardiac muscle fiber, the duration of the contraction is closely related to the duration of the action potential because of the calcium influx maintained during the plateau of the action potential. Thus, characteristics of the action potential can influence the duration and strength of the cardiac contraction.



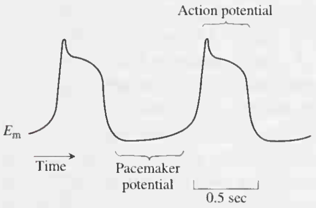
The pacemaker potential

Although the ionic mechanism of the cardiac action potential differs in important ways from that of other action potentials, nothing in the scheme presented so far would account for the endogenous beating of isolated heart cells discussed earlier. If we recorded the electrical membrane potential of a spontaneously beating isolated heart cell, we would see a series of spontaneous action potentials, as illustrated in Figure 13.7. After each action potential, the potential declines to its normal negative resting value, then begins to depolarize slowly. This slow depolarization, called a **pacemaker potential**, reflects spontaneous changes in the membrane ionic permeability.

Voltage-clamp experiments on single isolated muscle fibers from the ventricles suggest that the pacemaker potential arises from the combination of a slow decline in the potassium permeability and a slow increase in sodium and calcium permeability. When the depolarization reaches the threshold level, it triggers an action potential in the fiber. The rapid upstroke is caused by opening of sodium channels, and the prolonged plateau is produced by calcium channels.

Part of the early phase of the pacemaker potential represents the normal undershoot period of an action potential (see chapter 5), when potassium channels that were opened by depolarization during the action potential slowly close again. The membrane potential then moves in a positive direction, away from the potassium equilibrium potential. Later phases of the pacemaker potential reflect increases in sodium and calcium permeability, both of which move the membrane potential in a more positive direction, toward the sodium and calcium equilibrium potentials. Sodium permeability increases during the pacemaker potential, as nonspecific cation channels open at more hyperpolarized membrane potentials. As described in chapter 7, the opening of channels with equal permeability to sodium and potassium ions (like the acetylcholine-activated channels at the neuromuscular junction) produces cell depolarization. These hyperpolarization-activated cation channels open in response to the membrane hyperpolarization during the undershoot of the action potential. Together with the decrease in potassium permeability, the influx of sodium ions moves the membrane potential of the cardiac cell in a positive direction, toward the threshold for firing an action potential. As the membrane potential becomes more positive during the pacemaker potential, voltage-dependent calcium channels open in response to the depolarization. The resulting influx of positively charged calcium ions produces even greater depolarization, ultimately triggering the next action potential.

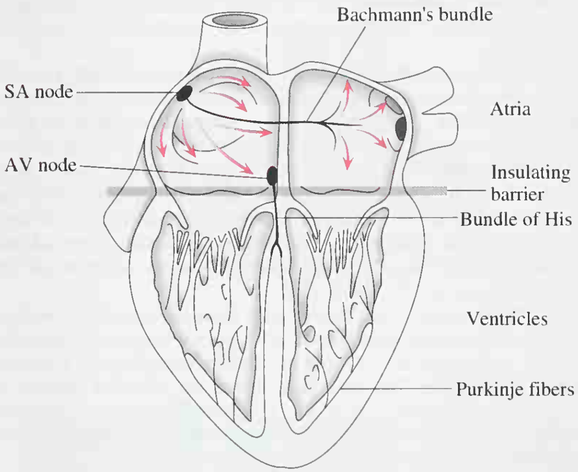
Figure 13.7
A recording of the membrane potential during repetitive, spontaneous beating in a single cardiac muscle fiber. The repolarization at the end of one action potential is followed by a slow, spontaneous depolarization called the pacemaker potential. When this depolarization reaches the threshold level, it triggers a new action potential.



The rate of spontaneous action potentials in isolated heart cells varies from one cell to another; some cells beat rapidly, while others beat slowly. In the intact heart, however, the electrical coupling among the fibers guarantees that all fibers contract together, with the overall rate being governed by the fibers with the fastest pacemaker activity.

In the normal functioning of the heart, the overall rate of beating is controlled by a special set of pacemaker cells, called the **sinoatrial (SA) node**, which is located in the upper part of the right atrium (Fig. 13.8). The action potential of cells in the SA node differs from that of other cardiac cells. In the SA node, calcium channels play a larger role than sodium channels in triggering the action potential and sustaining the depolarization during the action potential. In the normal resting human heart, the SA node cells generate spontaneous action potentials at a rate of approximately 70 per minute. These action potentials spread via the electrical connections among fibers throughout the two atria, generating a simultaneous contraction of the atria. The spread of excitation from the right atrium to the left atrium is facilitated by a bundle of muscle fibers, called Bachmann's bundle, that are specialized for more rapid conduction of excitation. This helps ensure that the two atria contract together. The atrial action potentials do not spread directly to the fibers making up the two ventricles, however. The contraction of the ventricles is delayed, allowing the relaxed ventricles to fill with blood pumped into them by the atrial contraction.

Figure 13.8
A diagram of the spread of action potentials across the heart during a single heartbeat. The excitation originates in the sinoatrial (SA) node of the right atrium and spreads throughout the atria via electrical coupling among the atrial muscle fibers. The spread is facilitated by special conducting fibers in Bachmann's bundle. The fibers of the atria are not electrically connected to those of the ventricles. The action potential spreads to the ventricles via the atrioventricular (AV) node, which introduces a delay between the atrial and ventricular action potentials. When the wave of action potentials leaves the AV node, its spread throughout the ventricles is aided by the rapidly conducting Purkinje fibers of the bundle of His.



In terms of electrical conduction, the heart behaves as two isolated units, as shown in Figure 13.8. The two atria comprise one unit, and the two ventricles make up a second unit. The electrical connection between these two units occurs via another specialized group of muscle fibers called the **atrioventricular (AV) node.** Excitation in the atria must travel through the AV node to reach the ventricles. The fibers of the AV node have a small diameter compared with other cardiac fibers. As discussed in chapter 5, action potential conduction is slower in small-diameter fibers. Therefore, conduction through the AV node introduces a time delay sufficient to retard the contraction of the ventricles relative to the contraction of the atria. Excitation leaving the AV node does not travel directly through the muscle fibers of the ventricles, but moves along specialized muscle fibers that are designed for rapid conduction of action potentials. These **Purkinje fibers** form a fast-conducting pathway through the ventricles called the **bundle of**

His. The Purkinje fibers carry the excitation rapidly to the apex at the base of the heart, where it spreads out through the mass of ventricular muscle fibers to produce the contraction of the ventricles.

Actions of acetylcholine and norepinephrine on cardiac muscle cells

Each muscle fiber of a skeletal muscle receives a direct synaptic input from a particular motor neuron; without this synaptic input, a skeletal fiber will not contract unless stimulated directly by artificial means. On the other hand, cardiac muscle fibers generate spontaneous contractions that are coordinated into a functional heartbeat by the electrical conduction mechanisms inherent in the heart itself. Nevertheless, the activity of the heart is still influenced by inputs from the nervous system, in the form of two opposing inputs that affect the heart rate.

One neural input comes from the cells of the parasympathetic nervous system, whose synaptic terminals in the heart release the neurotransmitter acetylcholine (ACh). The ACh slows the rate of depolarization during the pacemaker potential of the SA node. As a result, the interval between successive action potentials lengthens, slowing the rate at which this master pacemaker region drives the heartbeat. Acetylcholine acts by increasing the potassium permeability of the muscle fiber membrane, which tends to keep the membrane potential closer to the potassium equilibrium potential and thus retard the growth of the pacemaker potential toward the threshold for triggering an action potential.

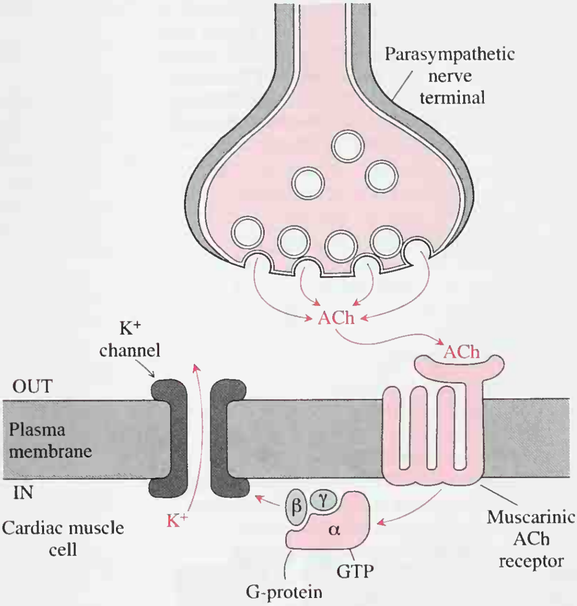
The second neural input to the heart comes from neurons of the sympathetic nervous system, whose synaptic terminals release the neurotransmitter norepinephrine. Activation of this input speeds the heart rate and increases the strength of contraction. This effect is mediated via increased opening of calcium channels during depolarization. Thus, the parasympathetic and sympathetic divisions of the autonomic nervous system have opposite effects on the heart, just as they do in all other target organs.

Acetylcholine and norepinephrine act indirectly on potassium channels and calcium channels, respectively. Recall that neurotransmitters can affect ion channels either directly (as is the case for ACh at the neuromuscular junction) or indirectly via intracellular second messengers (see chapter 8). In the heart, the acetylcholine released by the parasympathetic neurons binds to and activates a type of ACh receptor quite different from the nonspecific cation channel that is directly activated by ACh at the neuromuscular junction. This type of receptor is called the **muscarinic acetylcholine receptor** (because it is activated by the drug muscarine and related compounds, as well as by ACh). The ACh receptor at the neuromuscular junction is called the **nicotinic acetylcholine receptor** (because it is activated by the drug nicotine and related compounds).

Muscarinic receptors are not ion channels. Instead, the activated receptor binds to and stimulates GTP-binding proteins (G-proteins; see chapter 8) that are attached to the inner surface of the membrane near the receptors. The sequence of events that couple muscarinic receptors to potassium channels is summarized in Figure 13.9. In their active form, with GTP bound,

Figure 13.9

Acetylcholine indirectly opens potassium channels in cardiac muscle cells. This neurotransmitter, which is released from the synaptic terminals of parasympathetic neurons, binds to a postsynaptic receptor called a muscarinic ACh receptor. This receptor then activates G-proteins by catalyzing the replacement of GDP by GTP on the GTP-binding site of the G-protein. The activated G-protein, with GTP bound, interacts either directly or indirectly with the potassium channel, causing the channel to open and permitting efflux of potassium ions. In the drawing, the G-protein has three subunits, and GTP binds to only one of them, the alpha subunit. The other two subunits (beta and gamma) dissociate from the alpha subunit when GTP binds; they are thought to interact with the potassium channels.

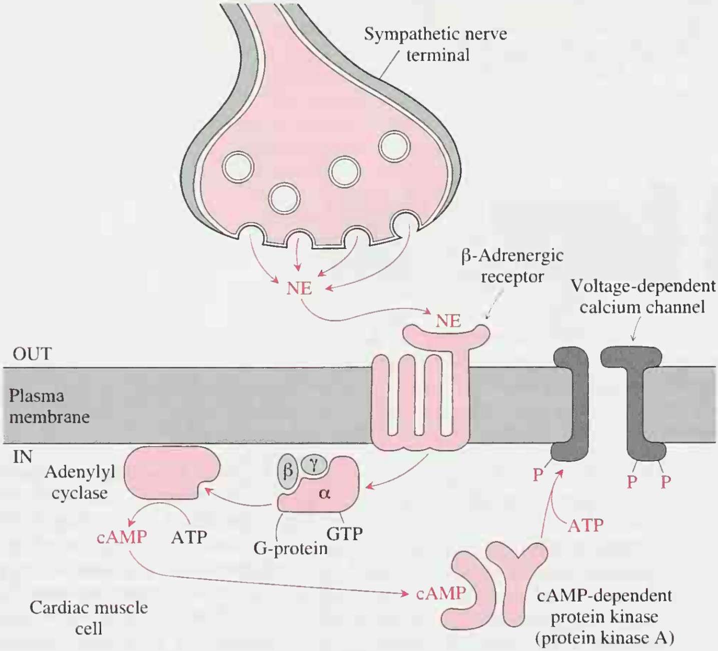


the G-proteins induce potassium channels to open, increasing the muscle cell's potassium permeability and slowing the rate of action potentials. The effect of the G-proteins on the channel may be direct (by binding of the channel protein to one or more subunits of the active G-protein) or indirect (by stimulation of arachidonic acid, a second messenger produced by enzymatic cleavage of membrane lipids). The muscarinic receptor activates the G-protein by stimulating the replacement of GDP by GTP at the GTP-binding site. The G-protein remains active—interacting with and opening potassium channels—as long as GTP occupies the binding site on the G-protein. The activity of the G-protein is terminated by the intrinsic GTPase activity of the G-protein itself, which ultimately hydrolyzes the terminal phosphate of the GTP, converting it to the inactive GDP.

The linkage between the norepinephrine receptor of the cardiac muscle cells and the calcium channels is also mediated via G-proteins, as summarized in Figure 13.10. The receptor on the cell surface that detects norepinephrine is a type called the **β-adrenergic receptor** (a class of norepinephrine receptor

Figure 13.10

Norepinephrine promotes the activation of voltage-dependent calcium channels in cardiac muscle cells. When norepinephrine is released from the synaptic terminals of sympathetic neurons, it combines with β-adrenergic receptors in the postsynaptic membrane of the cardiac muscle cells. The activated receptor stimulates G-proteins, which in turn activate adenylyl cyclase. This enzyme converts ATP into cyclic AMP. The cyclic AMP binds to and turns on protein kinase A, an enzyme that uses ATP as a phosphate donor to add a phosphate group to certain amino acids that form part of the calcium channel molecule. The phosphorylated calcium channel can be more readily opened upon depolarization and also remains open for a longer period. As a result, calcium influx increases during depolarization of the heart cell.



called the α-adrenergic receptor is also known, but is not involved in these effects of norepinephrine). β-Adrenergic receptors are members of the same family of receptors as the muscarinic cholinergic receptors. Like the muscarinic receptor, the β-adrenergic receptor is not itself an ion channel. Instead, it activates G-proteins inside the cell when norepinephrine occupies its binding site on the receptor. In the heart, the G-protein exerts its cellular actions by changing the level of **cyclic AMP** inside the cell. When the synthetic enzyme for cyclic AMP, **adenylyl cyclase**, is activated by the G-protein, it causes cyclic AMP levels to rise inside the cardiac cell. Cyclic AMP binds to and stimulates **protein kinase A** (also called **cyclic-AMP–dependent protein kinase**), which in turn attaches a phosphate group to (phosphorylates) specific amino acid groups of the calcium-channel protein. Phosphorylation of this channel is thought to be required before the calcium channel can open during depolarization; thus, an increase in cyclic AMP inside the cell translates into a greater number of operable calcium channels. In addition, each channel remains open for a longer time, on average, when it opens in response to depolarization. Thus, phosphorylation of the channels greatly potentiates the inward calcium current that flows during depolarization of the cardiac muscle cells.

In the SA node, the triggering of the action potential depends on calcium channels. If more calcium channels are available in the presence of norepinephrine, the threshold potential for triggering the action potential will be lower and the action potential will, therefore, be triggered earlier during the pacemaker potential. Outside of the SA node, in the muscle cells of the atria and ventricles, the calcium channels contribute to the plateau phase of the action potential and allow calcium influx, which then sustains the muscle contraction. An increase in the number of available calcium channels in these cells will increase the calcium influx during the plateau and thus increase the strength of contraction of the overall heart muscle.

The combination of the increase in heart rate and the increase in strength of contraction makes the β-adrenergic receptors powerful regulators of the amount of blood volume circulated per minute through the heart. As a result, the β-adrenergic receptors—which ultimately exert their effects by increasing the phosphorylation of voltage-activated calcium channels—are targeted by many drugs that are used clinically to increase the heart output in human patients whose heart muscles have been damaged by disease.

One advantage of having the autonomic neurotransmitters exert their actions through G-protein-linked receptors, rather than by direct binding to ion channels, is that the nervous system can produce relatively long-term effects on the ion channels of the heart without a continuing neural signal. Once the G-proteins are activated, they can affect channel activity for several seconds, until GTP is hydrolyzed by the G-protein and their activation terminates. Thus, ACh can be released briefly from parasympathetic nerve terminals (or norepinephrine from sympathetic nerve terminals) and still affect the heart rate for several seconds after ACh release terminates. If instead, ACh bound to and opened a ligand-gated potassium channel, the neurotransmitter would have to be present at all times to produce a long-lasting change in potassium permeability. Thus, the nervous system would have to send signals from the central nervous system to the autonomic ganglia continuously to stimulate a steady train of action potentials in the autonomic motor neurons. The somatic nervous system, for example, follows this pattern. Somatic motor neurons are tightly temporally coupled to the activation of their targets, the skeletal muscle fibers. This arrangement allows rapid, subsecond turn-on and turn-off of muscle activity under the control of the somatic nervous system.

In general, the targets controlled by the autonomic nervous system are involved in much slower activities that are typically sustained for longer periods. Therefore, the slower and more sustained activation produced by indirect linkage between neurotransmitter receptor and ion channels is well suited for the autonomic nervous system.

SUMMARY OF CARDIAC MUSCLE

The muscle fibers making up the heart are specialized in a number of ways to pump blood through the vessels of the circulatory system efficiently. These specializations lead to a number of differences between cardiac muscle fibers and skeletal muscle fibers (Table 13.1). In addition, the heart as an organ contains specific structures whose function is to coordinate the pumping activity, including the SA node, the AV node, and the Purkinje fibers. The SA node is the master pacemaker region of the heart, controlling the heart rate during normal physiological functioning. The AV node, which provides a path for electrical conduction between the atria and the ventricles, is responsible for the delay between atrial and ventricular contractions. The Purkinje

Table 13.1 Comparison of selected properties of skeletal and cardiac muscle fibers.

Property	Skeletal Muscle	Cardiac Muscle
Striated	Yes	Yes
Electrically coupled	No	Yes
Spontaneously contracts in the absence of nerve input	No	Yes
Duration of contraction is controlled by duration of action potential	No	Yes
Action potential is similar to that of neurons	Yes	No
Calcium ions make an important contribution to the action potential	No	Yes
Effect of neural input	Excite	Excite or inhibit
Division of nervous system that provides neural control	Somatic	Autonomic (parasympathetic and sympathetic)
Neurotransmitter released onto muscle fibers by neurons	ACh	ACh (parasympathetic) or norepinephrine (sympathetic)
Effect of neurotransmitter on postsynaptic ion channels	Direct	Indirect (via G-proteins)

fibers provide a rapidly conducting pathway for distributing excitation throughout the ventricles during the power stroke of a single heartbeat.

The activity of the heart is controlled by the sympathetic and parasympathetic divisions of the autonomic nervous system. Acetylcholine released by the parasympathetic nerve terminals in the heart causes the heart rate to slow by opening potassium channels. Norepinephrine released by the sympathetic nerve terminals increases the response of voltage-dependent calcium channels to depolarization, which then increases the rate of beating and the strength of contraction. Both effects of neurotransmitters are indirect, being mediated by receptors that act via GTP-binding proteins: muscarinic receptors in the case of acetylcholine, and β-adrenergic receptors in the case of norepinephrine. The β-adrenergic receptors increase the levels of cyclic AMP inside the cardiac cells, which in turn promotes phosphorylation of calcium channels by protein kinase A.

ORGANIZATION OF PREGANGLIONIC AUTONOMIC NEURONS

We will now consider the neural systems in the brain and spinal cord that control the peripheral autonomic ganglia. As noted previously, the motor neurons of the autonomic nervous system are located outside the central nervous system, in the autonomic ganglia. In the case of the heart, the sympathetic postganglionic neurons are located in sympathetic chain ganglia that parallel the spinal column in the cervical and upper thoracic regions. In keeping with the general rule that the parasympathetic postganglionic neurons are located in or near their target organs, the parasympathetic neurons of the heart are found in a diffuse network within the atrial muscles themselves. The preganglionic neurons of both the sympathetic and parasympathetic divisions are located in the central nervous system, but the anatomical organization of the preganglionic neurons differs for each division. The preganglionic organization is shown in Figure 13.11. The parasympathetic preganglionic neurons are located in the brain (in cranial nerve nuclei of the midbrain, pons, and medulla) and at the lowest levels of the spinal cord (in the sacral segments). The sympathetic preganglionic neurons are distributed along the spinal cord throughout the thoracic region and in the upper lumbar region.

Parasympathetic preganglionic neurons

The parasympathetic preganglionic neurons in the brain are associated with the nuclei of cranial nerves III (oculomotor nerves), VII (facial nerves), IX (glossopharyngeal nerves), and X (vagus nerves). The nuclei of the vagus nerves in the medulla are the dominant source of parasympathetic preganglionic fibers in the body. The vagus nerve distributes parasympathetic fibers to most of the viscera, including the heart, lungs, and abdominal organs. The nuclei of the glossopharyngeal nerves in the medulla and the facial nerves in the pons

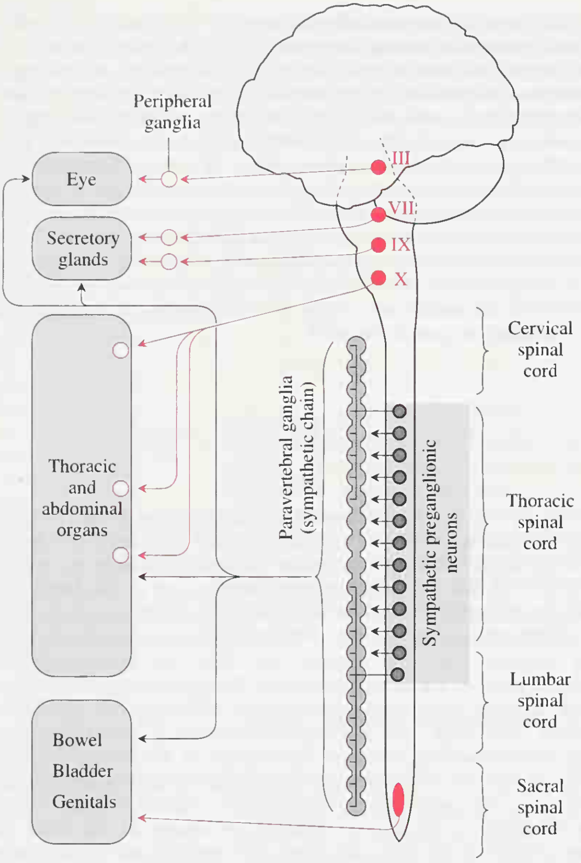


Figure 13.11
The locations of preganglionic neurons of the parasympathetic division (red) and the sympathetic division (gray) of the autonomic nervous system. The cranial nerve nuclei of nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus) contain the parasympathetic preganglionic neurons in the midbrain, pons, and medulla. These preganglionic neurons send fibers through the corresponding cranial nerves to peripheral parasympathetic ganglia in or near the target tissues (red circles). Parasympathetic preganglionic neurons are also found in the sacral part of the spinal cord. The preganglionic neurons of the sympathetic division are located in the gray matter of the spinal cord, distributed diffusely along the length of the cord from the thoracic to the lumbar region. The sympathetic preganglionic fibers travel along the chain of paravertebral sympathetic ganglia, extending several spinal segments above and below the position of the preganglionic neuron. For clarity, the figure shows the connections from only two spinal segments, but all segmental preganglionic fibers from each spinal segment have similar diffuse connections within the sympathetic chain of ganglia. In addition, the diagram omits the prevertebral sympathetic ganglia, which also receive direct synaptic connections from the preganglionic fibers exiting the spinal cord.

contain the parasympathetic preganglionic neurons controlling the secretory glands of the mouth, nose, and eye orbits. In the eye, parasympathetic innervation is controlled by parasympathetic preganglionic neurons of the oculomotor nuclei of the midbrain. At the other end of the central nervous system, in the sacral spinal cord, are the parasympathetic preganglionic neurons controlling the lower part of the bowel, the bladder, and the genital organs.

Like the parasympathetic postganglionic neurons, the parasympathetic preganglionic neurons release the neurotransmitter acetylcholine. Consequently, the locations of the parasympathetic preganglionic neurons can be revealed by stains that detect the presence of the synthetic enzyme for acetylcholine, choline acetyltransferase. In the oculomotor nucleus, for example, the parasympathetic preganglionic neurons are separate from, and just dorsal to, the somatic motor neurons that control the extraocular muscles. This is illustrated in Figure 13.12. The portion of the oculomotor nucleus that contains the parasympathetic preganglionic neurons is called the **Edinger-Westphal nucleus**.

Sympathetic preganglionic neurons

The sympathetic preganglionic neurons are located within the gray matter of the spinal cord (see Fig. 13.11). As is the case with somatic motor neurons, the axons of the preganglionic neurons exit the spinal cord via the ventral roots. At each vertebral segment, the preganglionic axons enter the connectives of the sympathetic chain and extend for some distance either anteriorly or posteriorly before making synaptic connections in paravertebral ganglia within the chain (see Fig. 13.11). As noted in chapter 10, the somatic motor neurons are located in the ventral, lateral portion of the gray matter (the ventral horn) in the spinal cord. Most of the sympathetic preganglionic neurons, however, appear at an intermediate position in the spinal gray matter, between the ventral and dorsal horns. This portion of the spinal cord is called the **intermediolateral gray matter** (shown in red in Figure 13.13). The cell bodies of the sympathetic preganglionic neurons form a diffusely organized column of cells (sometimes called the **intermediolateral cell column**) throughout the thoracic and upper lumbar spinal cord.

Most preganglionic axons of the sympathetic neurons immediately enter the paravertebral chain after exiting the spinal cord and make synaptic connections in paravertebral ganglia. However, some sympathetic preganglionic neurons instead send their axons to the prevertebral sympathetic ganglia, which innervate the abdominal organs and the sex organs. Another target of sympathetic preganglionic neurons is the adrenal gland. In this gland, the preganglionic fibers make excitatory synapses onto adrenal **chromaffin cells**, which secrete epinephrine* and norepinephrine into the bloodstream. The chromaffin cells may therefore be thought of as altered sympathetic postganglionic neurons, which have become specialized for an endocrine function (releasing transmitter into the circulation, thus reaching diffuse and diverse target organs) rather than for a typical neuronal function (releasing transmitter directly onto specific target organs).

Neighboring sympathetic preganglionic neurons within a spinal cord segment control the sympathetic innervation of diverse postsynaptic targets and produce physiological changes in widely distributed target organs. Particular regions of the body are not strictly mapped onto particular parts of

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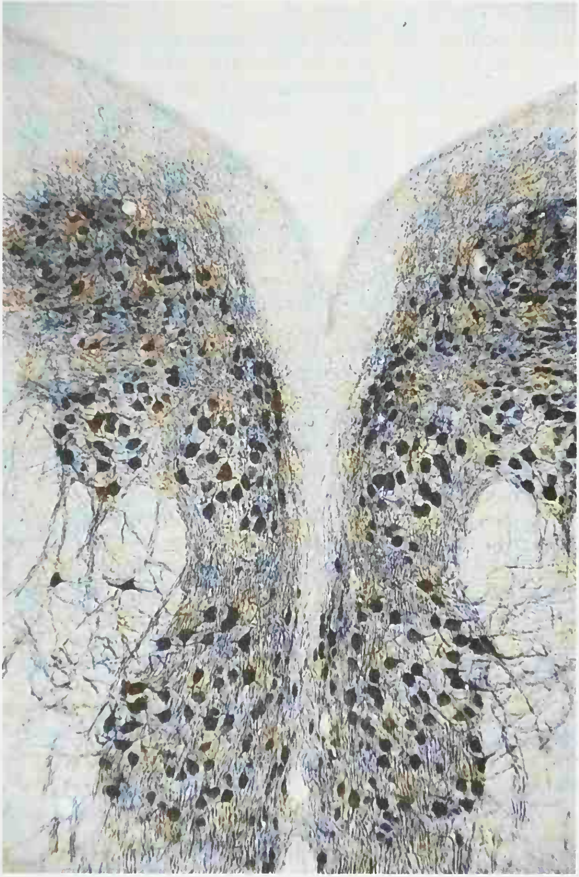
*The neurotransmitter/hormone epinephrine acquired its name because it was first isolated from the adrenal gland ("epinephrine" means "around the kidney," and the adrenal gland sits astride the kidney). An alternative name for epinephrine is *adrenaline,* a term also derived from the adrenal gland.

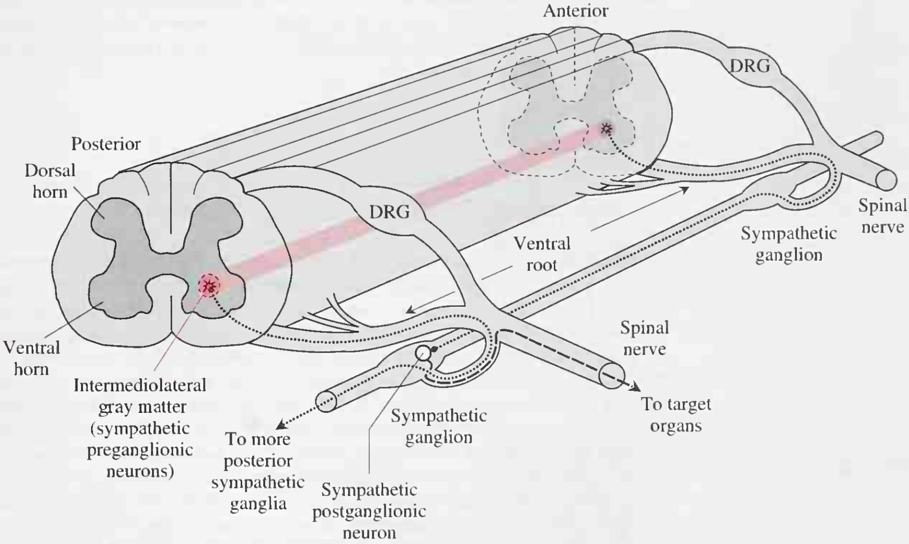
Figure 13.12

Neurons of the oculomotor nucleus, stained to reveal the presence of choline acetyltransferase, the synthetic enzyme for the neurotransmitter acetylcholine. The motor neurons in the lower part of the nucleus control the extraocular muscles, as discussed in chapter 12. The parasympathetic preganglionic neurons in the upper part form a subdivision of the oculomotor nucleus called the Edinger-Westphal nucleus, which projects to the peripheral parasympathetic ganglia of the eye.



Courtesy of J. T. Erichsen of the University of Wales.

Figure 13.13
The location of sympathetic preganglionic neurons within the gray matter of the spinal cord. The diagram shows two successive spinal segments. The cell bodies of the sympathetic preganglionic neurons are located at an intermediate level in the gray matter, called the intermediolateral gray matter (shown in red). The preganglionic neurons are scattered along the spinal cord in the intermediolateral gray matter, although the figure shows only two neurons, one at each spinal nerve exit point. The axons of the sympathetic preganglionic neurons (dotted lines) leave the spinal cord via the ventral roots and then exit from the spinal nerve to enter the paravertebral sympathetic chain. Within the sympathetic chain ganglia, the preganglionic axons make excitatory synapses with the sympathetic postganglionic neurons. The postganglionic axons (dashed lines) exit the ganglia and enter the spinal nerves to travel to their target organs in the periphery. For simplicity, the preganglionic neurons and sympathetic chain are shown for only one side of the spinal cord, although the same circuitry is duplicated on the other side.



the intermediolateral cell column. This scheme is, therefore, quite distinct from the organization of somatic motor neurons. The motor neurons that innervate a particular skeletal muscle are found near one another within a particular spinal cord segment, whereas the sympathetic preganglionic neurons whose corresponding postganglionic neurons innervate a particular organ are scattered along several segments. This organization is compatible with the diffuse activation or inhibition of many different organ systems required for the "fight-or-flight" function of the sympathetic nervous system.

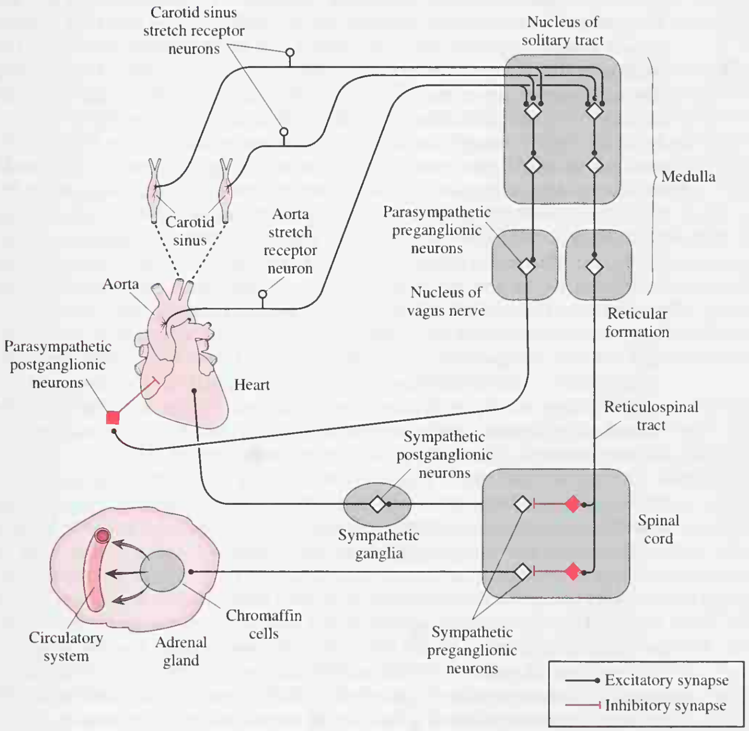
Like the parasympathetic preganglionic neurons, the sympathetic preganglionic neurons release the neurotransmitter acetylcholine. Both types of postsynaptic acetylcholine receptors—nicotinic and muscarinic—are found in the postganglionic neurons. The nicotinic receptors produce a fast excitatory postsynaptic potential via an increase in sodium and potassium permeability, as at the neuromuscular junction. The muscarinic receptors produce a slower excitatory postsynaptic potential that is produced indirectly via internal second messengers, as in the heart. Activating the muscarinic receptors closes a particular type of potassium channel that contributes to the regulation of repetitive action potential activity during prolonged depolarization. As a result, the postganglionic neuron becomes more likely to fire a train of action potentials during synaptic excitation, producing stronger activation of the sympathetic response in the target organs. In addition to acetylcholine, the synaptic terminals of the sympathetic preganglionic neurons contain a variety of neuropeptides that are thought to act as neurotransmitters, producing slow synaptic responses in the postsynaptic neurons via intracellular second messengers.

BRAINSTEM CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

One hallmark of the operation of the somatic nervous system is the presence of fast, intraspinal reflex loops that connect sensory information from the muscles to the skeletal motor neurons. In the case of the stretch reflex, this connection is as direct as possible, with the sensory neuron making a monosynaptic connection onto the motor neuron from the same muscle. In the case of the autonomic nervous system, however, the reflex loops are commonly much longer, and there is typically no direct connection between sensory neurons and the autonomic preganglionic neurons. In part, this arrangement accounts for the slow action of the autonomic nervous system on its target organs. Regulation of the output does not occur on a very rapid time scale, partly because sensory information reaches the autonomic preganglionic neurons only indirectly, via several relay stations. For the sympathetic preganglionic neurons in the spinal cord, for example, the controlling inputs come predominantly from descending axons that arise from neurons located in the brainstem.

An example of the organization of the autonomic reflexes is the **cardiac baroreceptor reflex** (Fig. 13.14). When blood pressure rises, the increased pressure is sensed by stretch receptor neurons whose nerve endings are located in the walls of the carotid artery in a specialized region called the **carotid sinus.** Additional stretch receptors innervate the walls of the aorta, the main artery leaving the heart. When blood pressure rises, the walls of the blood vessels expand, increasing the rate of action potentials in the stretch receptor neurons. Increased activity in these neurons reflexively decreases the sympathetic input to the heart and increases the cardiac parasympathetic

Figure 13.14
The cardiac baroreceptor reflex. Stretch receptor neurons innervate the arterial walls of the aorta and specialized regions of the carotid arteries, the carotid sinuses. These stretch receptors are activated by stretch of the artery wall produced by the blood pressure. These neurons then make excitatory connections onto neurons within the nucleus of the solitary tract in the medulla. The solitary tract neurons in turn project via additional interneurons to the parasympathetic preganglionic neurons of the heart, located in the nucleus of the vagus nerve, and to reticulospinal neurons that send axons to the spinal cord. Increased activity of the stretch receptors excites the parasympathetic preganglionic neurons, which then excite the parasympathetic neurons of the heart and increase the release of acetylcholine. The reticulospinal neurons excite interneurons in the spinal cord, which then inhibit sympathetic preganglionic neurons involved in control of the heart.


Carotid sinus stretch receptor neurons
Nucleus of solitary tract
Medulla
Carotid sinus
Aorta stretch receptor neuron
Parasympathetic preganglionic neurons
Aorta
Nucleus of vagus nerve
Reticular formation
Parasympathetic postganglionic neurons
Heart
Reticulospinal tract
Sympathetic postganglionic neurons
Spinal cord
Sympathetic ganglia
Chromaffin cells
Circulatory system
Adrenal gland
Sympathetic preganglionic neurons
Excitatory synapse
Inhibitory synapse

input. This process decreases heart rate and cardiac output, which then lowers blood pressure. Conversely, if blood pressure drops below normal, the arterial walls will be less stretched, and activity in the stretch-sensitive neurons declines. Inhibition of cardiac sympathetic preganglionic neurons in the spinal cord is reduced, as is the excitation supplied to the parasympathetic preganglionic neurons in the nucleus of the vagus nerve. Activity thus increases in the sympathetic innervation of the heart and decreases in the parasympathetic innervation, raising both heart rate and cardiac output. In this manner, the reflex maintains the arterial blood pressure at a particular level, adjusting heart rate and cardiac output to reflect changes in blood pressure.

The axons of the arterial stretch receptor neurons enter the brain in the medulla, where they make excitatory synapses on interneurons in the **nucleus of the solitary tract.** This nucleus is a multipurpose area that receives inputs from a variety of sensory systems and helps regulate automatic homeostatic functions of the body, including cardiac function. After passing through one or more excitatory interneurons within the nucleus of the solitary tract, the excitation that originated in the stretch receptor neurons is relayed to the parasympathetic preganglionic neurons of the heart, in the **nucleus of the vagus nerve** (cranial nerve X). These neurons then make excitatory synapses onto the parasympathetic postganglionic neurons in the heart, which release acetylcholine and inhibit cardiac activity by activating muscarinic cholinergic receptors. In addition, other interneurons in the nucleus of the solitary tract make excitatory synapses onto reticulospinal tract neurons in the medullary reticular formation. These neurons then project into the spinal cord, where they excite groups of interneurons that inhibit the sympathetic preganglionic neurons. This reduction in the excitation of the sympathetic pathway leading to the heart decreases norepinephrine release from sympathetic nerve terminals in the heart, even as acetylcholine release from the parasympathetic inputs is increasing. The release of epinephrine and norepinephrine from the adrenal chromaffin cells is also reduced via the same inhibitory pathway (see Fig. 13.14).

At the normal blood pressure, the walls of the arteries are somewhat stretched, so a certain level of action potential activity usually occurs in the stretch receptor neurons. This ongoing activity contributes a steady level of excitation to the cardiac parasympathetic pathway and a steady level of inhibition to the cardiac sympathetic pathway, by way of the synaptic connections shown in Figure 13.14. Of course, other sources contribute excitatory and inhibitory inputs to both the parasympathetic and sympathetic preganglionic neurons within the central nervous system. The net result is a normal level of action potential activity in the neurons of both the sympathetic and parasympathetic pathways, with the heart rate and cardiac output at any moment representing the sum of these competing influences. When arterial pressure falls below the normal level, the decreased activity of the stretch receptors reduces two factors: the excitation reaching the parasympathetic preganglionic neurons, and the inhibition reaching the sympathetic preganglionic neurons. The balance between the parasympathetic and sympathetic inputs to the heart then shifts to increase cardiac output and restore blood pressure. In this way, the baroreceptor reflex system opposes both increases and decreases in blood pressure from the normal "set-point" value.

SUMMARY

Motor systems of the nervous system can be classified into two divisions, based on the motor targets that they innervate. The somatic nervous system controls the skeletal musculature, and thus most of what we normally envision as the "behavior" of the organism. The autonomic nervous system controls other important organ systems involved in maintaining the internal homeostasis of the organism, including the cardiovascular system, the respiratory system, and the digestive system.

The two types of motor systems are organized differently. The motor neurons of the autonomic nervous system are located outside the central nervous system, in autonomic ganglia. The somatic motor neurons, by contrast, are located within the gray matter of the spinal cord and thus form part of the central nervous system. The autonomic nervous system is divided into the parasympathetic and sympathetic subsystems. The parasympathetic autonomic ganglia are located close to or in the target organs themselves. Thus, the postganglionic nerve fibers that extend from the neurons in the ganglia to the target organ are usually short in the parasympathetic division. The sympathetic ganglia are typically located close to the central nervous system, and most are found in two chains of ganglia, called the paravertebral ganglia, that parallel the spinal column on each side of the spinal cord. Thus, the postganglionic fibers that extend from the sympathetic ganglia to the target organs are relatively long.

The nerve terminals of the parasympathetic postganglionic neurons release the neurotransmitter acetylcholine in the target organ. Acetylcholine typically acts on the target cells by activating muscarinic cholinergic receptors, which exert their postsynaptic actions by altering the level of internal second messengers—such as cyclic AMP—in the postsynaptic cells. The nerve terminals of the sympathetic postganglionic neurons release the transmitter norepinephrine, which also exerts its postsynaptic effect by altering the levels of internal second messengers. In organs that receive both sympathetic and parasympathetic innervation, acetylcholine and norepinephrine usually have opposite effects on the target cells. In the heart, for example, acetylcholine decreases heart rate and reduces cardiac output, while norepinephrine increases heart rate and cardiac output.

The central nervous system controls the neurons of the autonomic ganglia via output neurons called preganglionic neurons. The parasympathetic preganglionic neurons are located in the brainstem and the sacral spinal cord. The parasympathetic preganglionic fibers exit the brain via cranial nerves III, VII, IX, and X and travel to the parasympathetic ganglia near or in the target organs. The sympathetic preganglionic neurons are located in the intermediolateral gray matter of the spinal cord, from thoracic to lumbar levels. Most of the preganglionic fibers that exit the spinal cord travel only a relatively short distance to enter the chain of paravertebral sympathetic ganglia on either side of the spinal column. Unlike many reflexes in the somatic nervous system, sensory input in autonomic reflexes reaches the preganglionic neurons only indirectly, after passing through a number of interneurons.

PART IV

Sensory Systems

In our description of motor systems in Part 3, we frequently mentioned the role played by sensory information in initiating and modulating motor output. In some cases, such as the muscle spindle and the vestibular organ, we found it necessary to describe the sensory side of the control system in some detail. Sensory information about the environment and about the state of the organism's own body represents the starting point for understanding much of the motor behavior of an animal. In the next part of the book, we will examine the portions of the nervous system devoted to obtaining and processing information about the environment—the sensory systems.

Chapter 14 introduces some general properties of sensory systems. The remainder of this part then examines the anatomical and physiological organization of specific sensory systems, with chapters devoted to each of the important sensory modalities. Chapter 15 explores the processing of information from the so-called somatic senses, which arise from receptors located in the skin and musculature. The somatic senses include touch, pressure, pain, and temperature, as well as sensations relating to muscle length, tension, and joint position. In chapters 16 and 17, we discuss the visual system—one of the important ways that animals gather sensory information about the environment from a distance. The auditory system is described in chapter 18 and the chemical senses (taste and olfaction) in chapter 19.

14

An Overview of Sensory Systems

Evolution has equipped the nervous system with a great variety of specialized subsystems designed to gather information about the environment. This information is required for the nervous system as a whole to coordinate the actions of the organism in ways that make sense for survival. In subsequent chapters in Part 4, we will examine in detail the functional organization of some of these neural sensory systems. First, however, it will be useful to introduce some general principles of sensory systems that apply across the board, regardless of the type of sensory information being gathered from the environment.

THE SENSORY RECEPTOR NEURON

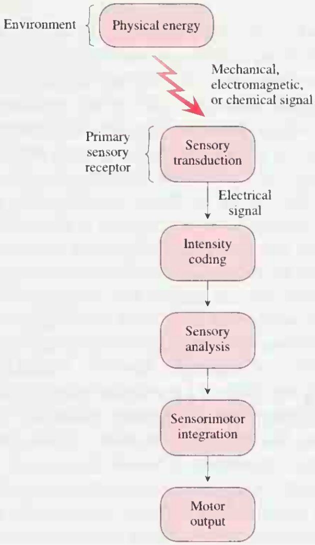
Sensory receptor neurons respond to particular types of stimulus energy

Information is transmitted and processed in the nervous system by electrical signals. For the nervous system to react to an environmental stimulus, the energy form of that stimulus must be translated into an electrical signal. This task is performed by the **sensory receptor neurons** (also called **primary sensory receptors**), which sit at the interface between the nervous system and the outside world. The properties of our sensory receptors govern which aspects of the environment we are aware of and which aspects pass completely unnoticed. When we watch a bat flying at dusk, for example, it appears to flit silently across the sky. In reality, however, the bat is shrieking frequently and loudly as it flies. Because the bat's high-frequency cries are beyond the range of human hearing, they are not a part of our sensory world.

Even for the parts of the environment we can detect, the properties of sensory receptors determine our level of sensitivity to stimuli, our ability to sense changes in intensity, and our adeptness at distinguishing qualitatively among different aspects of the stimulus. For example, humans normally perceive and identify colors based on the way light of a particular wavelength interacts differentially with the three different visual pigment molecules of the three types of cone photoreceptors found in the human retina (see chapter 16). If one class of visual pigment molecule is absent because of a genetic abnormality, then the affected individual cannot distinguish among all colors of light in the range normally perceived by humans. Conversely, if a fourth pigment were added, then a new and greater range of colors could be distinguished. Thus, everything the brain knows about the environment is filtered through the sensory receptors, and the sensory world of an organism is determined by the sensory cells with which it is endowed.

If an organism is able to respond to a particular type of environmental stimulus, then it must possess sensory receptors that are sensitive to the form of physical energy that constitutes the stimulus. Furthermore, the nervous system encodes the qualitative properties of a stimulus event based on the types of sensory neurons that are activated by the event. Activity in neurons connected to photoreceptors will be interpreted by the nervous system as providing information about light versus darkness, activity in neurons connected to muscle spindle receptors will be interpreted as giving information about muscle stretch, and so on. The perceived **modality** of a stimulus (that is, whether it is perceived as light, touch, pain, or another sensation) is governed by the type of sensory neuron activated by the stimulus.

Figure 14.1
The schematic organization of the steps in a typical neuronal sensory system. Physical energy impinges on the organism from the environment and acts on specialized primary sensory receptor neurons. These specialized cells translate the physical energy of the stimulus into an electrical signal, a process termed sensory transduction. The electrical signal in the receptor neuron is then translated into action potentials in the intensity-coding stage. The action potentials pass through several stages of sensory analysis to extract information about the environment, which is then combined with motor commands to control the organism's motor output.

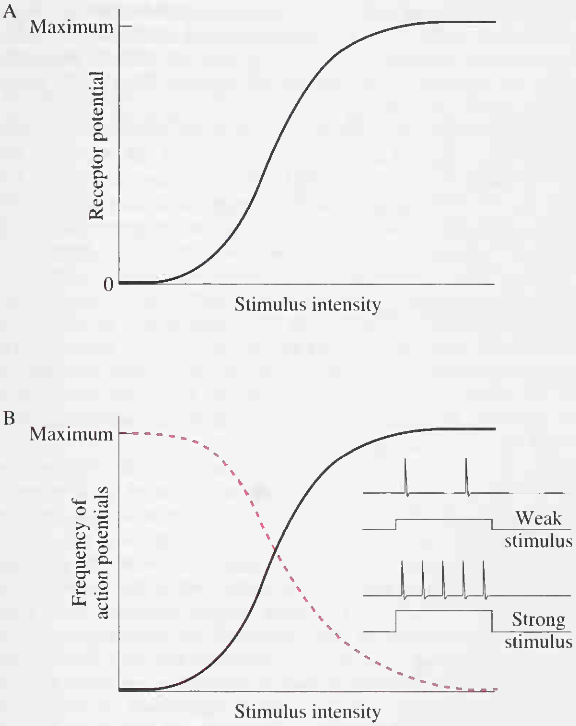


Coding of stimulus intensity

A generalized scheme for processing sensory information in the nervous system is summarized in Figure 14.1. When an event happens in the physical environment, an energy signal becomes available to interact with sensory receptors that are sensitive to that form of energy. The signal may be mechanical, as when the organism touches or is touched by an object in the environment (an "object" may include the molecules of air or water that transmit pressure waves that lead to the sensation of sound). In the case of vision, the signal energy is electromagnetic (photons of light of particular wavelengths). The signal may also be chemical, as in olfaction, taste, or monitoring of the chemical state of the blood. These signals are transformed into electrical signals through the process of **sensory transduction**, which is the first event in the generation of a sensory signal. The electrical signal generated in the sensory receptor is called the **receptor potential.**

In most cases, mere detection of the presence of a stimulus is not sufficient; instead, information about the strength of the stimulus is commonly desirable as well. In most sensory receptors, the receptor potential that results from the process of sensory transduction is graded according to the intensity of the stimulus. For example, a strong light gives rise to a large change in the membrane potential of the photoreceptors in the eye, while a weak light produces a correspondingly smaller change in membrane potential (see chapter 16). Figure 14.2A shows the relationship between amplitude of receptor potential and strength of sensory stimulus for a hypothetical sensory receptor neuron. As the stimulus intensity increases from its initial low level, the threshold intensity for the receptor is reached, and the receptor cell begins to respond. As the intensity increases further,

Figure 14.2
The coding of stimulus intensity in the nervous system. (A) In the primary sensory receptor neurons, the relevant stimulus produces a receptor potential whose amplitude increases with stimulus intensity. (B) The receptor potential influences the firing rate of action potentials, in either the primary receptor neuron or a secondary neuron receiving synaptic input from the receptor neuron. A weak stimulus produces action potentials at a low rate, while a strong stimulus produces action potentials at a rapid rate (see inset). The receptor potential can also reduce the firing rate of action potentials (dashed red line).



the amplitude of the receptor potential grows progressively larger, until it reaches its maximum. Thus, coding of stimulus strength is, to some extent, an inherent feature of the transduction process.

Electrical signals are transmitted over long distances in the nervous system by action potentials, and so the graded receptor potential in the sensory receptor neuron must ultimately be translated into action potential activity. The action potentials may be triggered in the primary receptor neuron itself or in a secondary sensory neuron (also called **second-order sensory neuron**) that receives synaptic input from the sensory cell. This process of **intensity coding** is the next step in sensory information processing (see Fig. 14.1). Action potentials are all-or-nothing events, as we discussed in detail in chapter 5. Once the receptor potential becomes sufficiently large to trigger an action potential, a further increase in the amplitude of the receptor potential will not be reflected in the amplitude of the action potential. Therefore, another coding mechanism is needed to signal the amplitude of the sensory stimulus. In many cases, the stimulus intensity is coded by the frequency with which the sensory neurons fire action potentials (as shown in the inset in Figure 14.2B). A weak stimulus causes a small receptor potential and triggers action potentials only rarely. A stronger stimulus produces a larger receptor potential and causes the sensory neurons to fire action potentials more often during the stimulus.

At stages subsequent to the generator potential, the stimulus intensity is encoded by the frequency of action potentials during the stimulus. This relationship is shown for a hypothetical sensory system in Figure 14.2B (black curve). Note that this graph also demonstrates that stimulus intensity can be encoded by either a *decrease* in ongoing action potential activity (dashed red curve) or an *increase* in action potential activity from a low baseline. That is, cessation of firing can signal the presence and intensity of a stimulus. In sensory systems, neurons that decrease their firing during a sensory stimulus (the "off" pathway) are frequently found in addition to neurons that increase their firing during a stimulus (the "on" pathway). The visual system is a good example of this principle (see chapter 16). Neurons downstream to the on and off pathways can obtain a sensitive indication of the stimulus intensity by comparing the level of action potential activity in the neurons of the on and off systems.

Stimulus intensity is also encoded by the population of sensory neurons activated by a stimulus. Strong stimuli will activate more of the total population than will weak stimuli. Thus, neurons involved in analyzing a sensory stimulus can obtain an indication of its intensity by pooling the activity across the whole population of sensory neurons sensitive to the stimulus. In addition, the sensitivity of individual receptors within the population of sensory neurons may vary for a particular sensory modality, with some being activated by weaker stimuli and others only by stronger stimuli. For example, sensory receptor neurons that innervate the skin demonstrate widely varying threshold levels of mechanical stimulation necessary to cause them to fire action potentials. Some respond to light touch or brushing of the skin, others react to strong pressure on the skin, and still others respond only to stimuli sufficiently strong to damage the skin. This variation is observed in even simple invertebrates, like the leech, and primitive vertebrates, like the lamprey.

Figure 14.3 illustrates responses of skin sensory neurons to mechanical stimulation in the lamprey. The most sensitive cells, called touch receptors, respond to gentle pressure or stroking of the skin (see Fig. 14.3A). The

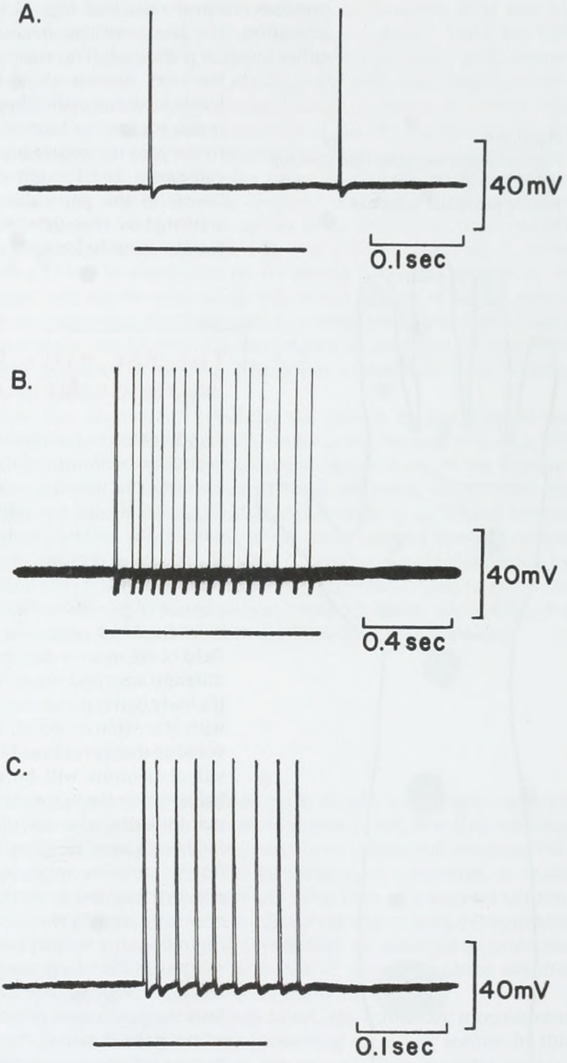
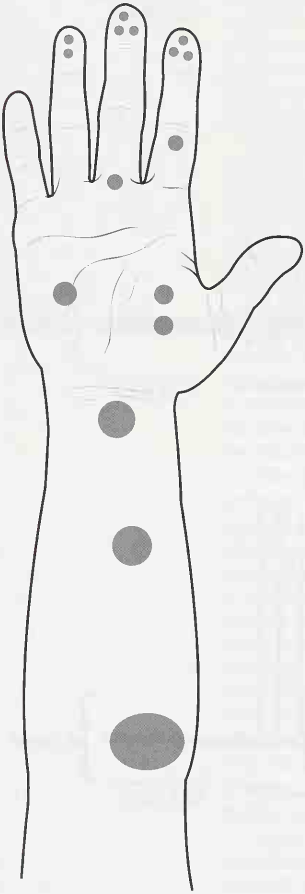


Figure 14.3
Examples of responses of skin sensory receptor neurons in the lamprey, a primitive vertebrate. The traces show intracellular recordings of membrane potential from a touch-sensitive neuron (A), a pressure-sensitive neuron (B), and a nociceptor neuron (C). Activity was stimulated by applying a blunt probe to the skin at the times indicated by the stimulus trace below each record of membrane potential. The pressure applied by the probe was very light for the touch receptor, moderate for the pressure receptor, and very strong for the nociceptor.

pressure receptor cells (see Fig. 14.3B) require stronger pressure for their activation. The least sensitive neurons (see Fig. 14.3C) do not respond to either touch or pressure, but do react to a stimulus that damages or penetrates the skin. Because these latter cells respond only to damaging levels of stimulation, they are called **nociceptors** (the Latin verb *nocere* means "to hurt or injure"); presumably, they correspond to the pain receptors found in humans. Thus, the nervous system can gauge the strength of mechanical stimulation of the skin, based on the particular populations of skin sensory neurons activated by the stimulus. This method of judging stimulus intensity often holds with other sensory modalities as well.

Figure 14.4
Representative receptive field sizes for light touch at different locations on the fingers, palm, and forearm.



THE RECEPTIVE FIELD OF PRIMARY RECEPTOR NEURONS

Another feature common to a variety of sensory modalities is revealed by examining the responses of individual skin sensory receptors. The pressure receptor cell whose response is shown in Figure 14.3B did not respond equally to pressure applied at all parts of the animal's body surface. Before the cell can respond to the stimulus, pressure must be applied to a small part of the skin, corresponding to the area where that particular neuron sends its peripheral processes. This portion of the skin where responses can be elicited in a particular sensory neuron is called the **receptive field** of the neuron. Receptive fields for skin sensory neurons have different sizes and shapes in different parts of the body. In general, if a body part is particularly important for an animal in interacting with the external world, then many sensory neurons will be devoted to that part of the body, and the receptive fields for the individual neurons will be relatively small. For example, human beings and other primates use their hands for many purposes in manipulating the environment. Consequently, the receptive fields of touch receptor neurons that innervate the palm and fingers are quite small, as shown in Figure 14.4. This fact is important, because a particular sensory neuron signals a touch occurring anywhere within its receptive field. A neuron receiving input from the sensory neuron cannot tell the location within the receptive field where the touch occurred. Having a large number of small receptive fields among the primary sensory neurons allows the population of second-order sensory neurons to construct a fine-grained map of the object being manipulated by the hand. In contrast, the receptive fields of the touch-sensitive sensory neurons are larger on the skin of the forearm, and even larger on the back and the trunk. For this reason, the fingertips can easily distinguish two closely spaced objects, but the forearm cannot.

You can readily demonstrate this difference in receptive field size on yourself, using two blunt pencils (not sharp ones, please). Hold the two pencils together with their points in the same horizontal plane, as illustrated in Figure 14.5. If you touch the two pencils gently with your fingertip (with your eyes closed), you can readily perceive two distinct points of contact with the finger. The arrangement of receptive fields of the touch-sensitive sensory neurons of the fingertip makes this distinction possible, as illustrated schematically in Figure 14.5A. Although the figure includes only three sensory receptor neurons (for simplicity), the fingertip is actually innervated by a large number of such neurons. The receptive fields are so small that sensory neuron A will selectively be stimulated by the pressure of pencil 1, while sensory neuron C will be stimulated by the pencil 2. Sensory neuron B, on the other hand, will not be stimulated. When this pattern of action potentials reaches the brain and the information is analyzed in the skin sensory systems of the brain (see chapter 15), the pattern of activation of the three sensory receptors gives rise to your perception of two points of contact, separated by an unstimulated region.

Now repeat the experiment, touching the pencils to the skin on the underside of the forearm (the underside works better because it is typically less hairy). This new situation is diagrammed in Figure 14.5B. In the forearm, the receptive fields of the skin sensory neurons are much larger, and both pencil tips fall within the receptive field of sensory neuron A. Sensory neuron B remains unstimulated. The neurons of the brain sensory systems cannot discern that the action potentials in sensory neuron A were stimulated by two separate contact points, rather than a single contact point. Thus, the receptive field size of the primary sensory neurons limits the ability of a sensory system to discern small spatial variations in a stimulus object.

LATERAL INHIBITION

The actual arrangement of the receptive fields of adjacent sensory neurons on the skin is not as simple as that shown in Figure 14.5A. In reality, adjacent fields from different skin sensory neurons show substantial overlap. This overlap might be predicted to blur the localization of a stimulus, as touch applied to any location would then activate more than one receptor neuron. However, the synaptic interconnections among the higher-level neurons that receive inputs from the primary sensory receptors are arranged to overcome this blurring action and enhance the detection of stimuli occurring simultaneously at two closely spaced positions on the skin.

In the wiring diagram given in Figure 14.6A, the inhibitory interneurons shown at the second level of sensory processing are a key feature in this system. The second-order neurons that receive excitatory synaptic connections from the primary receptor neurons not only send axons to higher sensory centers in the brain, but also connect with local inhibitory interneurons. The inhibitory interneurons in turn make inhibitory synapses

Figure 14.5
The receptive field size determines the organism's ability to discern closely spaced stimuli. In this experiment, two pencils are held together so that their points are in the same plane and are touched to the skin on the finger or the forearm. (A) Using the fingertip, we can readily discern the two pencil tips. Each touch receptor neuron innervates a small piece of skin in the fingertip, creating a small receptive field for each receptor. (B) In the forearm, the receptive fields of individual neurons are larger. The two pencil points fall within a single receptive field and thus cannot be distinguished.

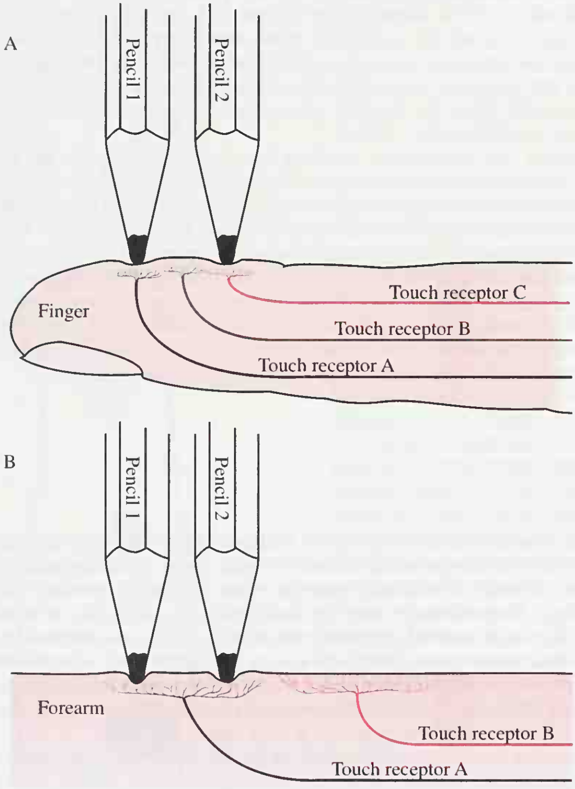
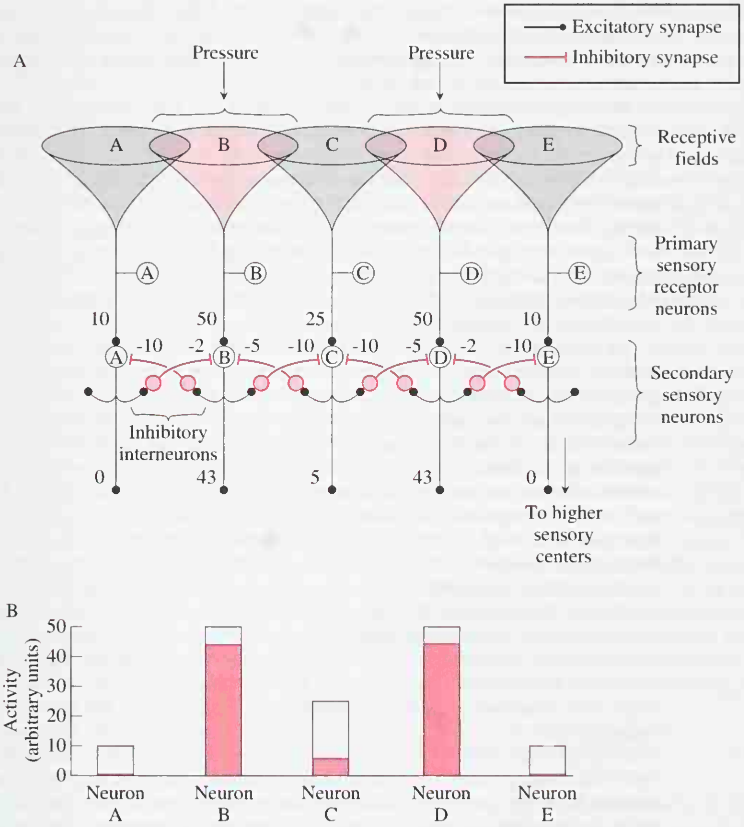


Figure 14.6
The effect of lateral inhibition on the ability to discriminate two closely spaced stimuli applied to the skin. (A) A schematic diagram of the connections from five primary sensory receptor neurons (labeled A–E) to their corresponding second-order sensory neurons in the central nervous system. The overlapping receptive fields of the neurons in the skin are shown above. The numbers next to each neuron indicate the amount of excitatory activity (in arbitrary units) produced by the two stimuli. (B) A bar graph showing the amount of activity in the primary receptor neurons (unshaded) and in the secondary neurons (red).



onto the second-order neurons receiving connections from the *adjacent* primary sensory receptors. In this manner, the activity in a particular pathway (corresponding to a particular receptive field) feeds back to subtract from the activity in adjacent pathways. Because the inhibitory connections are made with the pathways to the side, this process is termed **lateral inhibition.** This feature is found in information processing in most sensory systems, not just in the skin sensory system.

Consider the specific example shown in Figure 14.6A. Suppose that two stimuli are applied to the skin in such a way as to fill the receptive fields of two receptor neurons, at positions B and D in the figure. These two neurons will be maximally activated and will fire action potentials corresponding to 50 arbitrary units of excitation arriving at their synapses with the second-order neurons in the central nervous system.

Because of the overlapping receptive fields, the two stimuli will also activate the three other receptor neurons at positions A, C, and E. The stimuli fall on only a portion of these receptive fields, however, so these three neurons have less activity than the neurons at positions B and D. Suppose sensory receptor neurons A and E fire action potentials at a rate corresponding to 10 arbitrary units of excitation at their respective excitatory synapses with their second-order neurons. The receptive field of sensory receptor neuron C is partially activated by both stimuli, so its activity will be somewhat higher (although still not maximal), corresponding to 25 arbitrary units of excitation in our example.

To calculate the outputs of the second-order neurons, we must also evaluate the effect of the lateral inhibitory connections. For illustrative purposes, let us assume that the strengths of the excitatory and inhibitory connections in the lateral pathways are arranged so that the inhibitory connection to each side arising from a particular pathway produces enough inhibition to subtract 20% of the driving excitation from the primary sensory neuron of that pathway. For instance, second-order neuron B receives 50 units of excitation from its primary neuron and supplies 10 units of inhibition (that is, 20% of 50) to its neighboring second-order neurons (A and C). Second-order neuron C receives only 25 units of excitation from its primary neurons and subsequently supplies 5 units of inhibition (20% of 25) to its neighbors. The net result is shown graphically in Figure 14.6B for both the primary sensory neurons (unshaded bars) and the secondary neurons (red bars). The second-order neurons whose corresponding receptive fields are maximally stimulated (B and D) receive much excitation but little inhibition from their neighbors, whose corresponding receptive fields are not maximally stimulated. Conversely, the second-order neurons that are not maximally stimulated receive relatively little excitation but greater inhibition from their highly active neighbors. Overall, lateral inhibition enhances the contrast between the second-order neurons receiving inputs from the maximally activated primary receptors and the neighboring pathways originating from adjacent receptive fields.

Notice that the shaded bars in Figure 14.6B (corresponding to the activity in the second-order neurons) differ from one another more than the unshaded bars (corresponding to the activity in the primary sensory neurons).

In this way, the lateral inhibitory connections accentuate the differential activity present in the array of primary sensory receptors, enhancing the demarcation between stimulated and unstimulated regions. Lateral inhibition is also a prominent feature of synaptic processing in the visual system, where it serves to accentuate the boundary between light and dark portions of the visual world (see chapter 16).

Another common feature of sensory systems is also highlighted by our discussion of the circuitry of lateral inhibition. In Figure 14.6A, the primary sensory receptors connect in an orderly way with the second-order neurons, allowing the array of receptive fields of the primary receptors to be retained in the spatial organization of the second-order neurons. The receptor surface (the skin, in our example system) forms a two-dimensional map on the "surface" of the second-order neurons, which is then retained as information is passed through relay stations to the sensory portions of the cerebral cortex (see next chapter). This **somatotopic mapping** of the peripheral sensory system onto the neural systems involved in sensory processing in the brain is analogous to the somatotopic motor map of the body in the motor cortex (see chapter 11). In chapter 12, we saw a similar mapping of the retina surface onto the superior colliculus during sensorimotor integration in the oculomotor system.

As in the motor system map in the motor cortex, the representation of the skin in the internal sensory map in the brain does not depend on the actual surface area of the skin in different body regions. Instead, the representation in the map depends on the number of receptor neurons that innervate a particular region of the skin. As a result, parts that have small receptive fields and thus large numbers of neurons per square centimeter of skin area receive a correspondingly larger representation in the sensory map in the central nervous system. Again, although our example concerns sensory receptors of the skin, this principle holds for other sensory systems as well.

A related concept is the involvement of sensory channels in the processing of sensory information in the central nervous system. In Figure 14.6A, neighboring touch-receptive regions of the skin are segregated into neighboring pathways, or channels, in the subsequent processing of sensory information in the brain. These pathways form spatially coherent information channels, an arrangement that simplifies the wiring of the inhibitory connections underlying lateral inhibition. Local inhibitory interneurons can then form synaptic connections with all neighboring, through-conducting second-order neurons and thus create the appropriate circuitry without elaborate identification schemes that would be required if the information channels were randomly intermixed.

Lateral inhibition alters the receptive fields of higher-order sensory neurons

As noted previously, the receptive field of a neuron is defined as that portion of the sensory surface where stimuli affect the neuron's activity. For the primary sensory receptor neurons of the skin, this area corresponds to the portion of the skin contacted by the receptor endings of the neuron. The receptive field for higher-order neurons, however, will differ from that of the primary receptor, because of the synaptic interactions mediated by the inhibitory interneurons that produce lateral inhibition. Figure 14.7 illustrates this change in receptive field.

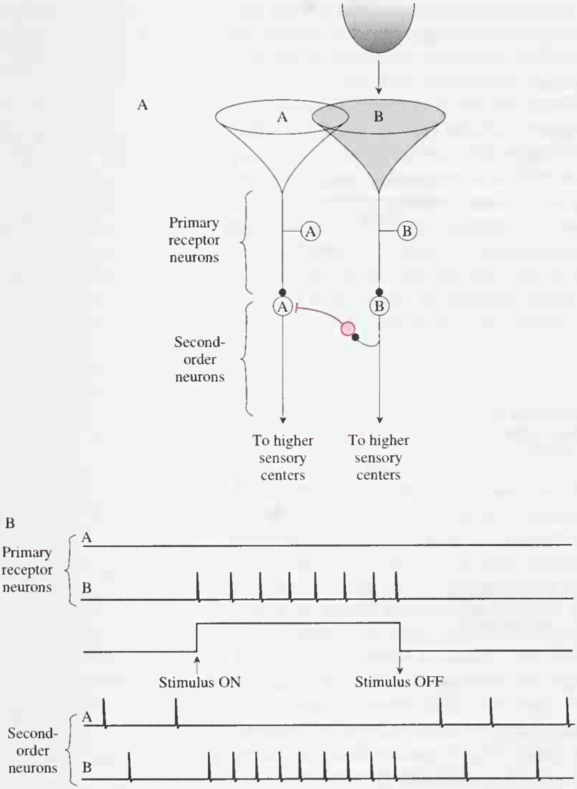
When a stimulus is applied to the receptive field of a skin receptor neuron (receptor B in Figure 14.7), it triggers a series of action potentials in that receptor at a frequency that depends on the intensity of the stimulus. If the stimulus is small enough to be confined predominantly to the receptive field of a single receptor (as in the figure), the neighboring receptor (receptor A) will not fire because the stimulus occurs outside its receptive field. The second-order neuron that receives a direct synaptic input from receptor B will therefore be strongly excited and will increase its firing rate strongly (see Fig. 14.7B).

Now consider the effect that the stimulus in receptive field B will have on the second-order neuron that receives input from primary receptor neuron A, whose receptive field is next door. Most secondary and higher-order sensory neurons fire action potentials at a moderate or low rate, even when a sensory stimulus is absent. Thus, they demonstrate a baseline level of activity. (This activity is referred to as "spontaneous" firing, although it arises predominantly from combined excitatory effects of synaptic inputs coming from neurons in other parts of the brain and thus represents a basal level of excitation.) Primary sensory neurons, by contrast, are typically silent except when a stimulus is presented to their receptive field (see Fig. 14.7B). When second-order neuron B fires strongly during the stimulus, it sends a strong inhibitory input to second-order neuron A via the lateral inhibitory interneuron, causing second-order neuron A to cease firing. The activity in the second-order neuron is thus influenced by stimulation in a wider area of the skin than the primary receptors.

By definition, then, the receptive fields of the second-order neurons differ from those of the primary receptors themselves. At each stage of synaptic processing, as sensory information is relayed through the brain, the receptive fields of the neurons may be altered substantially from the receptive fields of the neurons at the next lower stage. This feature is found in many types of information processing—not just that related to skin sensory information.

If we moved the stimulus probe in Figure 14.7 from receptive field B to A, then the situation would be reversed. The activity in second-order neuron B would be reduced by the stimulus, and second-order neuron A would be excited. The presence of the lateral inhibitory connections not only enlarges the receptive fields of the second-order neurons, but also qualitatively differentiates them from those of the primary receptor neurons. The receptive field of the second-order neuron is organized into an excitatory central region, surrounded by a concentric inhibitory region. This is illustrated in Figure 14.8. Moving the stimulus progressively across the skin surface, we can map out the receptive field of the primary receptor and the second-order neuron. The graph in Figure 14.8A summarizes the different behavior patterns of the neurons. As discussed previously, the firing rate of the receptor neuron increases as the stimulus enters the receptive field, and then declines as the stimulus exits on the opposite side of the receptive field (the black line in Figure 14.8A). When viewed from above, the receptive field of the primary receptor appears uniformly excitatory and has an area delimited by the

Figure 14.7
Second-order sensory neurons respond to stimuli outside the receptive field of the primary sensory neuron to which they are directly connected. This response reflects the lateral inhibitory connections among second-order neurons. (A) A schematic diagram of the synaptic circuitry. The stimulus is applied to the skin in the receptive field of primary sensory neuron B. (B) Action potential activity during the stimulus in the primary sensory neurons (above) and in the second-order sensory neurons (below).



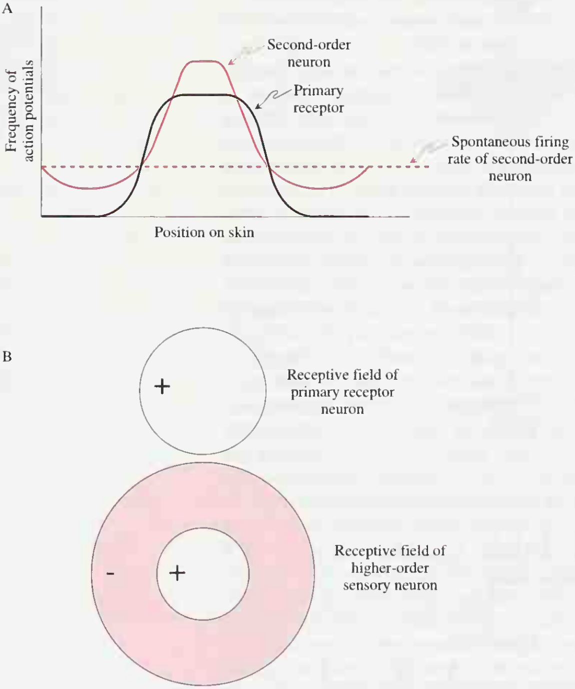

A
Frequency of action potentials
Second-order neuron
Primary receptor
Spontaneous firing rate of second-order neuron
Position on skin
B
+
Receptive field of primary receptor neuron
-
+
Receptive field of higher-order sensory neuron

Figure 14.8
Receptive fields of primary and second-order sensory neurons differ because of lateral inhibition. (A) The frequency of action potentials recorded in a primary sensory neuron (black line) and in the corresponding second-order neuron (red line) in response to a stimulus applied to various positions on the skin. The dashed line shows the frequency of "spontaneous" action potentials in the second-order neuron in the absence of stimulation. (B) The view from above the receptive fields of the primary sensory neuron (above) and the second-order neuron (below). A plus sign indicates that stimuli in that region excite the neuron; a minus sign indicates that stimuli in that region inhibit the neuron.

spread of the receptor's sensory processes in the skin (see Fig. 14.8B). In contrast, the firing rate of the second-order neuron initially falls below the baseline rate as the stimulus moves across the skin, because of the lateral inhibitory effect originating from the receptive fields of neighboring receptors. The firing rate then increases as the stimulus enters the receptive field of the receptor that makes a direct excitatory connection with the second-order neuron. Finally, the firing rate declines again when the stimulus passes out of this central portion of the receptive field and enters the inhibitory surrounding area on the other side.

Figure 14.8B shows a view from above of the receptive field of the second-order neuron, illustrating the inhibitory surround region and the excitatory central region. Note that the central, excitatory portion of the receptive field of the second-order neuron is smaller than the purely excitatory receptive field of the primary receptor. This size discrepancy arises because of the spatial overlap of neighboring receptive fields of the primary receptors (see, for example, Fig. 14.6). A stimulus near the edge of the field produces relatively weak excitation of the receptor, but stronger excitation of the neighboring receptor. The net result will be inhibition of the second-order neuron. Only when the stimulus moves into the central portion of the receptive field will the direct excitatory connection from the primary receptor outweigh the inhibitory influence from the surrounding receptors. This sharpening of the excitatory portion of the receptive field represents another important function of the lateral inhibitory connections—increasing the spatial resolution of the sensory system. The increased resolution arises because the second-order neurons effectively compare the amount of activity in a cluster of neighboring receptors. Subsequent sensory centers in the brain that receive connections from the second-order neurons will then be better able to localize the stimulus on the skin than would be expected from the sizes of the receptive fields of the primary sensory receptors themselves.

ADAPTATION

Another feature common to sensory receptors is that they respond best to *changes* in stimuli. During the sustained presence of a constant stimulus, the response of the receptor typically diminishes or ceases altogether in a phenomenon known as sensory **adaptation.** In the lamprey touch-receptor neuron (see Fig. 14.3), for example, the touch receptor fired only a single action potential at the very onset of the stimulus and did not fire again—even though the stimulus probe remained in contact with the skin for some time. This example illustrates the behavior of a rapidly adapting sensory receptor. The lamprey neuron also fired another action potential when the probe was removed from the skin. This response to stimulus removal is commonly seen in touch-receptor neurons, which might more properly be called skin-disturbance detectors that respond to change in skin indentation within their receptive fields. The pressure-receptor neuron fired a train of action potentials during indentation of the skin (see Fig. 14.3), indicating that this particular type of skin sensory neuron adapts more slowly than the touch receptor. Looking carefully at the figure, however, you can see that the interval between successive action potentials lengthened during the sustained stimulus; in other words, the frequency of firing declines progressively. Thus, the pressure receptor also shows adaptation during sustained stimulation.

The sensory receptors are our windows on the external world, and everything we know about our environment is governed by the outputs of those receptors. If the frequency of action potentials from the receptors declines during a sustained stimulus, our perception of the magnitude of the stimulus diminishes in tandem. For example, you can readily feel the pressure exerted by a watchband on your wrist when you first put on a wristwatch, but your perception of the pressure disappears within seconds because of receptor adaptation. Sensory adaptation is also readily apparent in the visual system. If you go from a dark movie theater to afternoon sunlight, you are initially dazzled by the brightness; within minutes, however, your visual system adapts to the new conditions and the brightness of the light no longer seems overwhelming.

Sensory adaptation stems from two sources. First, adaptation occurs during the sensory transduction process in the primary receptors themselves. During a sustained stimulus, the amplitude of the receptor potential declines. This drop is then reflected in a decline in the frequency of action potential triggered either in the primary receptors or in the neurons receiving synaptic input from the receptors. Second, adaptation results from changes in the synaptic interactions among neurons in the sensory system at various levels after the primary receptor. For instance, the amount of neurotransmitter released from presynaptic terminals per action potential may decline during a sustained train of action potentials, a phenomenon called synaptic depression. Even in the absence of synaptic depression, the postsynaptic response may decline during sustained activity because of postsynaptic changes mediated by slow accumulation of internal second messengers or by synaptic feedback from other neurons. Collectively, these nonreceptor forms of adaptation are termed **neural adaptation.**

CLASSIFICATION OF SENSORY RECEPTOR TYPE

Sensory receptors can be classified into broad categories based on the source of the sensory stimulus. For the most part, we have discussed sensory cells that receive and translate stimuli from the world outside of the organism. Sensory receptors that monitor the external environment are called **exteroceptive receptors** (or exteroceptors); they include the visual receptors, hearing, touch, smell, and so on. Other receptors, called **interoceptive receptors** (or interoceptors), monitor the internal environment of the organism; they include the blood-pressure sensors of the carotid sinus (see chapter 13). Finally, **proprioceptive receptors** (or proprioceptors) monitor the position of the body in space or the position of joints and muscles. Examples include the familiar muscle-spindle stretch receptors, which form the sensory pathway of the patellar stretch reflex, and the gravity sensors of the vestibular apparatus (see chapter 12).

Receptor neurons can also be classified based on the type of sensory stimulus to which they respond, regardless of the source of the stimulus. In this chapter, we have focused on receptors that respond to mechanical displacement, known as **mechanoreceptors.** The muscle-spindle receptors, the Golgi tendon organs, the touch and pressure receptors, and vestibular hair cells are all examples of mechanoreceptors. The sensory cells of the visual system that translate light energy into electrical signals are called **photoreceptors. Chemoreceptors** are cells that detect and respond to chemical substances, whether they originate outside the body (for example, olfactory receptors) or inside the body (for example, oxygen sensors in the circulatory system). As described earlier, **nociceptors** respond to tissue damage and give rise to the sensation of pain. Although the aspect of tissue damage to which these receptors are responding remains unknown, they may actually constitute a class of chemoreceptors that detect substances released by damaged cells or as part of local inflammatory responses to damage. The skin contains other receptors, called **thermoreceptors,** that respond to skin temperature (either hot or cold). Some species of fish, especially those that live in murky water, can detect the weak electrical fields generated in the water by the activity of the muscles of other fish. This information is used to locate prey or mates and, in some instances, is used for communication. The receptor cells that detect the electrical fields are called **electroreceptors.**

SUMMARY

Sensory systems are parts of the nervous system that detect and analyze stimuli from the external and internal environments of the organism. Primary receptor neurons are the cells at the interface between the environment and the nervous system. Through the process of sensory transduction, these neurons translate mechanical, chemical, or light energy from the environment into an electrical signal that can be passed along and analyzed in the nervous system.

Sensory stimuli generate electrical signals called receptor potentials in the primary receptor neurons. The receptor potential, which is graded according to stimulus intensity, stimulates action potentials in either the primary sensory neurons or second-order neurons that receive synaptic input from the primary receptor. The intensity of the stimulus is encoded by the frequency of action potentials, with more intense stimuli causing a higher rate of firing.

The receptive field of a sensory neuron is defined as the portion of the relevant sensory surface where receipt of a stimulus affects the activity of the neuron. The receptive fields of second-order and higher neurons are determined by two factors: the set of sensory receptors to which they are connected and lateral inhibitory interactions. Lateral inhibition serves to improve the spatial resolution of the sensory system. Receptive fields of second-order and higher neurons commonly have a concentric organization, with a central excitatory region surrounded by a ring-shaped inhibitory region. Sensory receptors typically show adaptation during sustained application of a stimulus, with the response of the sensory cell diminishing even though the stimulus remains the same.

15

The Somatic Senses

In chapter 14, we described some of the properties of the sensory receptor neurons that innervate the skin. In chapter 10, we discussed the response properties of muscle spindle organs and Golgi tendon organs. To this point, our discussion of these sensory receptors has focused on their roles in spinal reflex circuits involved in motor control. In this chapter, we will consider how other neural systems in the spinal cord and brain analyze the sensory information arising from the skin and muscle receptors.

SOMATOSENSORY RECEPTORS

Skin receptors

Collectively, the neural pathways concerned with the processing of signals arising from the receptors of the skin, muscles, and joints are called the **somatosensory** pathways. Several types of sensory receptors contribute to the somatosensory system. Figures 15.1 and 15.2 summarize the receptor types found in the human somatosensory system. When activated, each receptor type produces a specific type of sensation, called the **sensory modality.** Some receptors give rise to the sensation of touch, some to the sensation of pressure, and still others to pain. As we saw in our discussion of lamprey skin sensory neurons in chapter 14, the skin receptors can be distinguished based on the strength of stimulation required to excite them and on their adaptation characteristics. In human skin, the same distinctions can be made.

In addition to these functional differences, there are anatomical differences in the types of sensory endings formed by the receptor neurons within the skin (see Fig. 15.1). The touch- and pressure-sensitive mechanoreceptors form specialized structures within the skin that help to determine the response properties of the receptor neuron. Three types of mechanoreceptors have nerve endings that terminate within fibrous capsules, called **corpuscles.** The **Pacinian corpuscle** and the **Meissner corpuscle** are both very sensitive to touch and pressure, and both adapt rapidly during a sustained stimulus. Thus, these mechanoreceptors predominantly signal changes in stimulus intensity. Because of their rapid adaptation, both Pacinian and Meissner corpuscles are particularly sensitive to vibrating stimuli. A third type of encapsulated mechanoreceptor, the **Ruffini corpuscle**, is also sensitive to touch and pressure but adapts slowly during sustained stimuli. Another type of slowly adapting mechanoreceptor is the **Merkel receptor,** whose endings are not encapsulated but instead form a spray of disk-shaped endings in the

Figure 15.1
A summary of the receptor types found in human skin. Not all parts of the skin contain all of the receptor types depicted. The density of receptors also varies in different regions of the skin.

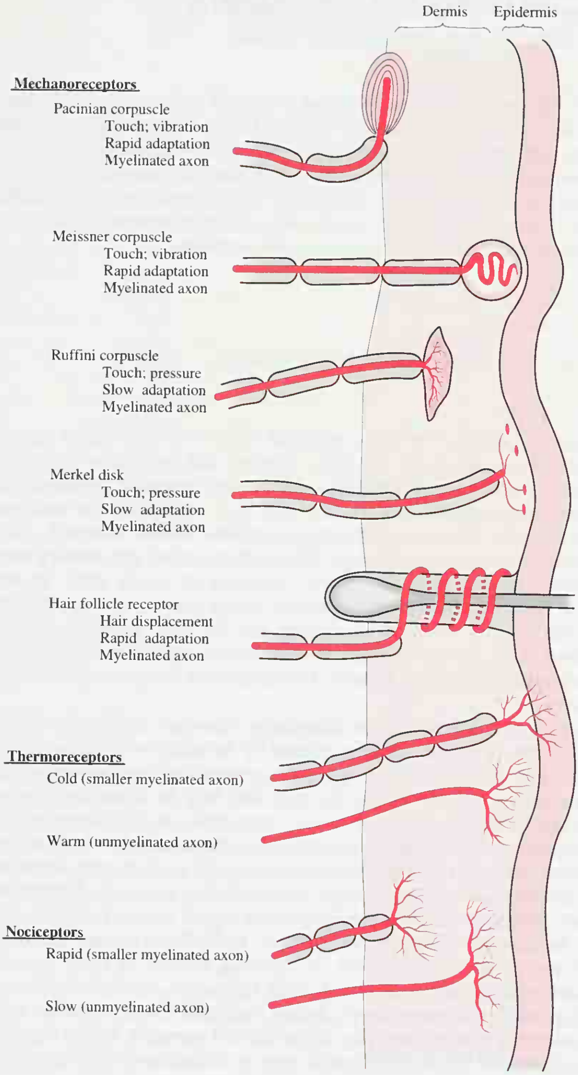
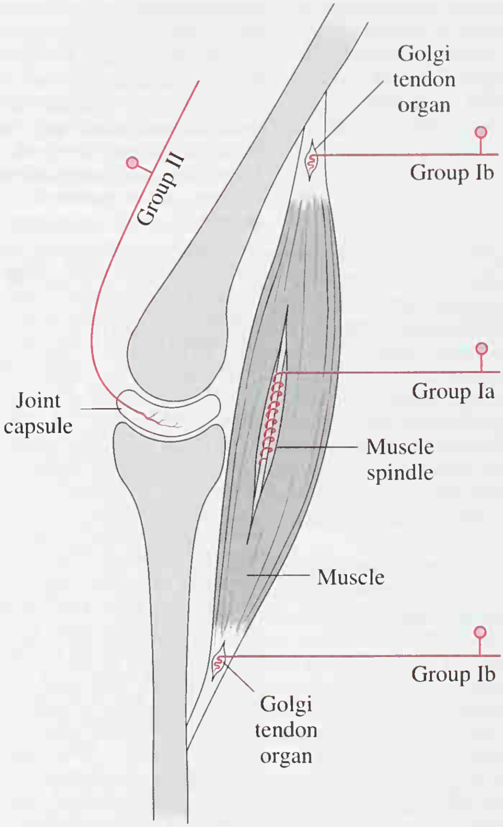


Figure 15.2
A summary of the receptor types involved in proprioception. The muscle spindle and the Golgi tendon organ of skeletal muscles were discussed in chapter 10. In addition, the joint capsule receives sensory innervation from sensory neurons that respond to changes in joint angle.



skin (Merkel disks; see Fig. 15.1). Because of their slowly adapting responses, the Merkel disks and the Ruffini corpuscles are well suited for encoding the intensity of a maintained pressure applied to the skin. A fifth type of mechanoreceptor, the **hair follicle receptor**, is found in hairy skin. These nerve endings spiral around single hair follicles and fire a rapidly adapting burst of action potentials upon deflection of the hair originating from that follicle.

The axons of all skin mechanoreceptor neurons have a moderately large diameter and are myelinated. The conduction velocity of these axons is in the range of 30 to 70 m/s, which is a bit slower than the larger-diameter axons of the muscle spindles (**group Ia**, 75–120 m/s) and the Golgi tendon organs (**group Ib**, 50–100 m/s; see chapter 10). The medium-size myelinated axons of the mechanoreceptors are called **group II.** (An alternative terminology for this group is **group Aβ**, with the faster-conducting muscle receptor axons being **group Aα**.)

In the skin mechanoreceptors, the transduction mechanism that couples mechanical stimulation to a change in ionic conductance of the membrane remains poorly understood. Mechanical deformation of the membrane is known to cause a depolarization (the **receptor potential**), which in turn activates action potentials in the nerve fiber of the sensory neuron. This receptor potential arises when mechanosensitive nonspecific cation channels open in the membrane of the sensory nerve ending. As with the opening of acetylcholine-sensitive nonspecific cation channels at the neuromuscular junction (see chapter 7), the resulting increase in sodium and potassium permeability generates a depolarization. Exactly how the deformation of the membrane induces the channels to open remains a mystery, however. Ion channels that are activated by membrane stretch have been recorded in a variety of cell types, including neurons. The channel protein is thought to be physically connected to the cytoskeleton, so that movement of the membrane relative to the cytoskeleton either increases or decreases tension applied to the channel molecule. This change in tension presumably induces a conformation change in the channel, causing it to open and conduct ions.

Mammalian skin is also innervated by **thermoreceptor neurons**, whose endings are particularly sensitive to the temperature of the skin (relative to body temperature). Two types of thermoreceptors have been identified (see Fig. 15.1). One class is excited when the skin is cooled below the resting body temperature. These **cold receptors**, which have myelinated axons that conduct more slowly than those of the mechanoreceptors, are members of conduction **group III** (or **group Aδ**). The second class of thermoreceptors increase their firing rates when the skin is warmed above the resting body temperature. The axons of these **warm receptors** are unmyelinated and thus conduct action potentials relatively slowly (less than 1 m/s) compared with myelinated fibers. The unmyelinated axons form conduction **group IV**, the slowest class of conduction speed. The unmyelinated axons are also called **C-fibers**, a term derived from the alternative name **group C** for the slowest-conducting axons in peripheral nerves. The thermoreceptors have no specialized sensory structures in the skin; instead, their axons form numerous fine branches called **free endings.** The process by which changes in skin temperature give rise to receptor potentials in the free endings of thermoreceptor neurons is unknown.

The **nociceptors** are the final class of sensory receptors found in the skin. These neurons fire when the skin is damaged in some way. They can be activated by pinching or puncture of the skin or by administering damaging levels of heat (skin temperatures greater than 45°C). Nociceptor activity produces the sensation of pain in humans. Nociceptors have either unmyelinated or small-diameter myelinated axons. The faster-conducting, myelinated nociceptors (group III or group Aδ) provide the sensory stimulus for activation of the withdrawal reflex (see chapter 10). These nociceptors give rise to the flash of searing pain we perceive immediately when a wound occurs. The slow-conducting class of nociceptors with unmyelinated axons produce the long-lasting burning pain that persists after the damage is done (the pain we feel from a sunburn is a mild example of this sensation). As with the thermoreceptors, the axons of the nociceptors terminate as free endings in the skin. These free endings are thought to detect chemical substances that are released from damaged tissue, meaning that the nociceptors may represent a type of chemoreceptor. The exact way in which the receptor potential in nociceptors is generated remains unclear.

Proprioceptive receptors

In addition to the sensory information arising from the receptors in the skin, the somatosensory pathways of the spinal cord and brain also deal with sensory information related to joint and limb position. Collectively, this type of sensory information is called **proprioception.** Proprioceptive information arises from the sensory receptors shown in Figure 15.2. The muscle spindle and the Golgi tendon organ, for example, give information about muscle length and muscle tension, as we saw in our discussion of spinal reflex circuits in chapter 10. In addition, mechanoreceptors that innervate the **joint capsule** give information about the angle of the skeletal elements at each point of articulation. The intrafusal muscle fibers of the muscle spindle are innervated by group Ia sensory fibers, the Golgi tendon organs are innervated by slightly slower-conducting group Ib sensory fibers, and the joint capsules are innervated by sensory axons of group II.

In mammals, the muscle spindle contains two different types of intrafusal muscle fibers, called **nuclear bag** and **nuclear chain** fibers. The group Ia sensory axon innervating the muscle spindle makes annulospiral endings (called **primary endings**) on both types of muscle fiber within the spindle. In addition, the nuclear chain fibers receive a second spiral ending (called a **secondary ending**) from a smaller-diameter sensory axon of group II. The primary and secondary sensory neurons respond differently to stretch of the muscle. The secondary ending provides a steady discharge that reflects the steady-state stretch of the nuclear chain fibers (and thus the overall length of the muscle). The primary ending also has a steady discharge that signals the steady-state length, but its discharge increases dramatically when the length changes (see chapter 10). Thus, the secondary sensory neuron signals the static length of the muscle, while the primary sensory neuron signals the change in length during stretch. To reflect these functional differences, the primary sensory fiber is also called the *dynamic* fiber and the secondary sensory fiber is termed the *static* fiber.

SPINAL ORGANIZATION OF SOMATOSENSORY PATHWAYS

The cell bodies of the sensory neurons that provide the sensory information described above are located just outside the spinal cord in the dorsal root ganglia. The axons of these neurons enter the spinal cord via the dorsal roots and make synaptic connections that underlie the various spinal reflexes discussed in chapter 10. In addition, the sensory information must be transmitted to the higher centers in the brain, where it is further analyzed and integrated with other sensory and motor information.

The ascending axons of the sensory neurons on their way to the brain are located in the white matter of the spinal cord. Axons representing the different sensory modalities are located in different parts of the white matter. The axons of neurons that carry information about touch, pressure, and vibration are found mostly in the **dorsal columns** (Fig. 15.3). Information from proprioceptors is also carried by dorsal column axons. Most myelinated sensory axons located in the dorsal columns are branches of the primary sensory neurons themselves. As the axons of the sensory neurons innervating the touch and pressure receptors of the skin enter the spinal cord via the dorsal roots, they bifurcate, as shown in Figure 15.4. One branch enters the gray matter locally to make synaptic connections with local spinal interneurons and directly with motor neurons. The other branch enters the dorsal columns on the same side of the spinal cord and ascends into the brain. Thus, some of the skin mechanoreceptor neurons in the dorsal root ganglia can have extraordinarily long axons that reach from the receptive field in the skin (at the tip of the toe, for example) to the brain. In addition, the dorsal columns contain axons originating from interneurons in the dorsal part of the gray matter that receive direct synaptic connections from the primary sensory neurons. These second-order neurons also carry information from the touch, pressure, and vibration receptors, as well as proprioceptive information (see Fig. 15.4).

Another important group of ascending sensory axons is found in the **lateral sensory tract** of the spinal cord (see Fig. 15.3). Unlike the dorsal

Figure 15.3
The locations of ascending sensory pathways in the white matter of the spinal cord. The major pathways are the dorsal columns, the spinocerebellar tracts, and the lateral sensory tracts. The diagram depicts a cross section through the spinal cord at the cervical level.

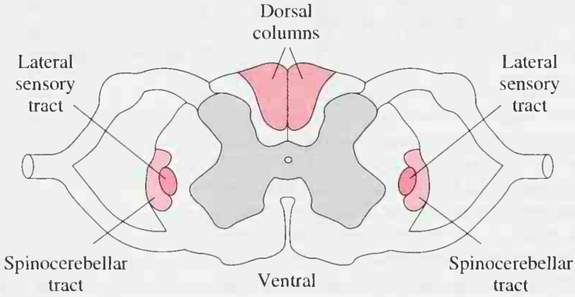
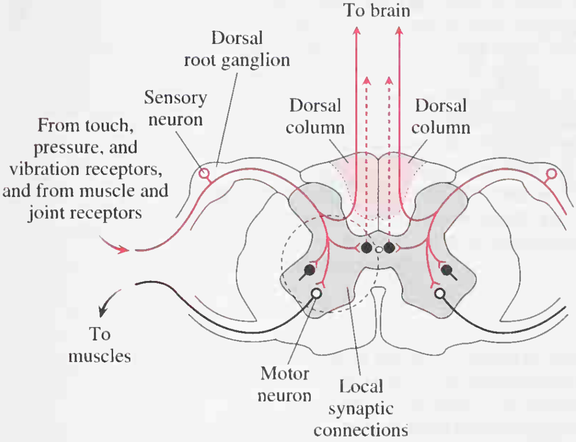


Figure 15.4
The projection pattern of sensory information in the dorsal columns of the spinal cord. Tactile and proprioceptive sensory neurons (red) in the dorsal root ganglia send axons into the spinal cord gray matter. There, synaptic connections are made directly onto motor neurons (as in the patellar reflex, for example) and onto a variety of spinal cord interneurons (black). In addition, the axon of the sensory neuron sends a branch into the white matter of the dorsal column on the same side of the spinal cord. This axon ascends in the ipsilateral spinal cord to the brain. A smaller fraction of the ascending axons in the dorsal columns (dashed red) originate from the interneurons contacted by the primary sensory neurons.


To brain
Dorsal root ganglion
Sensory neuron
From touch, pressure, and vibration receptors, and from muscle and joint receptors
Dorsal column
Dorsal column
To muscles
Motor neuron
Local synaptic connections

column sensory projections, which mainly consist of axon branches of primary sensory neurons, the axons in the lateral sensory tract are predominantly those of interneurons found in the dorsal part of the spinal cord gray matter. These interneurons receive synaptic inputs from pain- and temperature-sensitive sensory neurons. The axons of the interneurons cross the midline of the spinal cord before entering the lateral sensory tract in the lateral column on the opposite side of the spinal cord (Fig. 15.5). Thus, the ascending lateral sensory tract on one side of the spinal cord carries pain and temperature information from the opposite side of the body. In dorsal columns, the tactile and proprioceptive information on each side of the spinal cord comes from the same side of the body (compare the projection patterns shown in Figures 15.4 and 15.5). In addition, some interneurons that receive synapses from tactile sensory neurons also send axons into the ascending lateral sensory tract. Thus, tactile and proprioceptive information can reach the brain via either the lateral sensory tract or the dorsal columns, although the latter is the dominant path.

Figure 15.5
The projection patterns of sensory information in the lateral sensory tracts. Pain- and temperature-sensitive sensory neurons in the dorsal root ganglia send axons into the spinal cord via the dorsal roots. The sensory axons make synaptic connections with interneurons in the gray matter, whose axons then cross the midline and ascend in the contralateral lateral column. Although the figure includes only projections for one side of the spinal cord, the same set of projections is present on both sides.

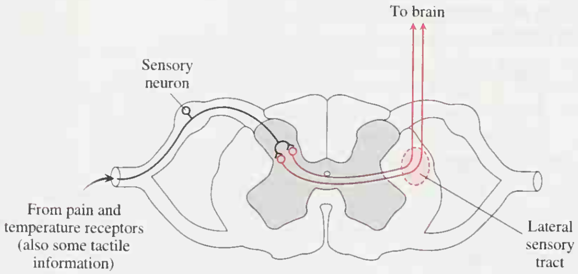
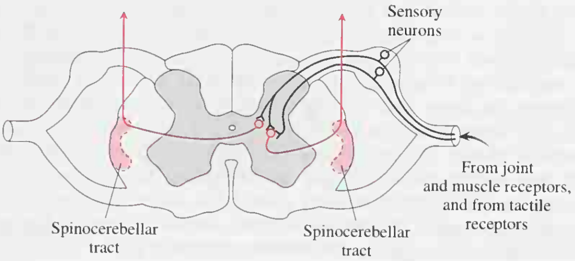

To brain
Sensory neuron
From pain and temperature receptors (also some tactile information)
Lateral sensory tract

Figure 15.6
The projection patterns of sensory information in the spinocerebellar tracts. Information to the cerebellum is provided by primary sensory neurons of joint and muscle receptors and tactile receptors. The sensory neurons are located in the dorsal root ganglia and send axons into the spinal cord via the dorsal roots. Synaptic contacts are made with interneurons in the spinal cord gray matter. The interneurons (red) project to the cerebellum via the spinocerebellar tracts in the lateral columns (pink), on either the contralateral side or the ipsilateral side of the spinal cord. Note that one of the interneurons illustrated receives inputs from two different sensory neurons. Although the figure shows only connections on one side of the spinal cord, the same set of projections is present on both sides.



As we discussed in chapter 11, the cerebellum is concerned with modulating reflex activity and modifying outgoing motor commands from other brain regions based on the outcome of ongoing motor actions. This activity requires sensory information about joint and muscle position, as well as tactile information about the body's contact with the environment. Much of this information comes from the sensory receptor neurons of the dorsal root ganglia. The ascending tracts that carry the sensory information from the spinal cord to the cerebellum, called **spinocerebellar tracts**, are located in the lateral portions of the lateral columns (see Fig. 15.3). As with the lateral sensory tract, the axons in the spinocerebellar tract come not from the primary sensory neurons themselves, but from interneurons in the spinal cord gray matter. Some of these interneurons send their axons across the midline of the spinal cord to ascend in the contralateral spinocerebellar tract; others remain on the same side and ascend in the ipsilateral tract (Fig. 15.6).

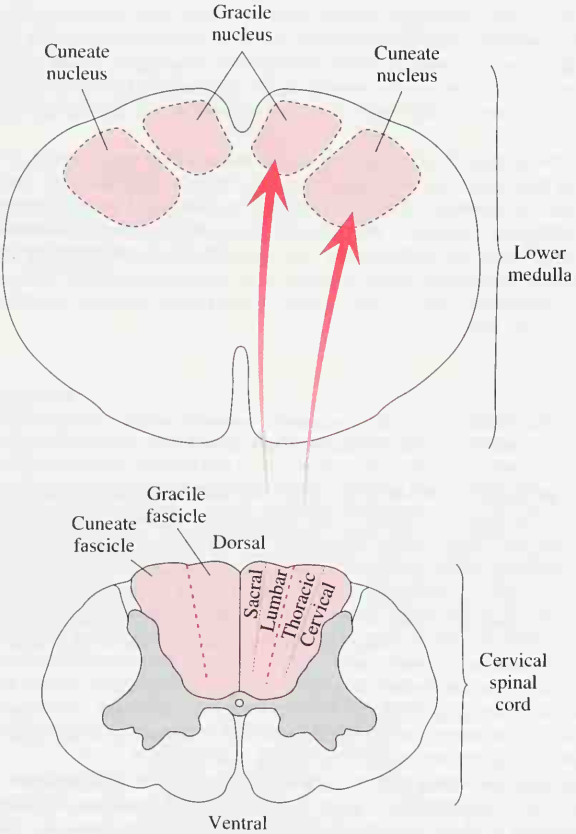
Some interneurons that give rise to the spinocerebellar tract receive synaptic inputs from more than one type of sensory neuron (see Fig. 15.6). Such interneurons can provide information about a confluence of sensory events, which might prove important for the cerebellum in its task of modulating motor output based on performance. For example, limb contact with the ground during locomotion might produce both tactile stimulation (contact with the environment) and muscle stretch, as load from the body weight is transferred to the limb.

BRAINSTEM RELAY STATIONS

During the evolution of the vertebrate brain, the brainstem was originally the sole "cerebral ganglion" responsible for modulating the responses of spinal reflex circuits and central pattern generators on the basis of sensory information. In primitive living vertebrates, such as the lamprey, the brainstem continues to serve this function, with the integrating centers of the brainstem reticular formation being the principal targets of the ascending sensory information from the spinal cord. As the cerebellum, midbrain, and forebrain became larger and more functionally complex during brain evolution, however, the older brainstem circuits were retained and modified. Thus, the sensory axons ascending from the spinal cord make a variety of synaptic linkages in the brainstem, before the information is passed on to the higher sensory processing centers in the newer parts of the brain.

The principal ascending path for tactile and proprioceptive information is the dorsal column, which consists predominantly of axon branches of primary sensory neurons. As these ascending axons leave the spinal cord and pass into the lower medulla, they enter and terminate in groups of interneurons located near the dorsal surface of the medulla, as shown in Figure 15.7. There are two such groups of interneurons on each side of the spinal cord: the **gracile nucleus** nearer to the midline, and the **cuneate nucleus** in a more lateral

Figure 15.7
The projections of the dorsal columns into the dorsal column nuclei of the lower medulla. The more medial portions of the dorsal columns, containing axons that originate at the sacral and lumbar spinal levels, send axons to the gracile nucleus on the same side of the brain. The lateral portions of the dorsal columns, containing axons of sensory neurons at thoracic and cervical spinal levels, project to the cuneate nucleus on the same side of the brain.



position. Together, these interneurons are referred to as the **dorsal column nuclei**, to reflect their roles as the targets of the ascending axons of the dorsal columns. The gracile nucleus on each side of the medulla receives axons from the more medial portions of the dorsal column of the ipsilateral spinal cord, while the cuneate nucleus receives axons from the more lateral portions of the dorsal column on the same side (see Fig. 15.7). As we ascend the spinal cord from the sacral end, sensory axons are added successively at the lateral edge of the dorsal columns at each vertebral segment. Thus, at the cervical end of the spinal cord, we find a medial–lateral organization of sensory axons, based on the spinal segment of origin (see Fig. 15.7).

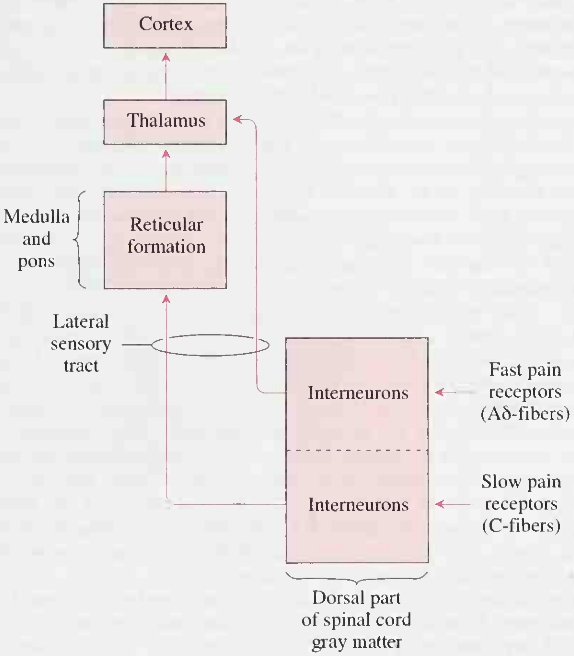
Because the sensory neurons of the lower limbs, lower trunk, upper trunk and limbs, and neck and face enter the spinal cord at successively higher vertebral segments, the medial–lateral organization shown in Figure 15.7 translates into a sensory map of the body surface. The lower parts of the body are represented at medial positions in the map and the upper parts of the body appear at more lateral positions. This **somatotopic map** is carried over into the synaptic projection to the dorsal column nuclei, with the lower portion of the body represented in the gracile nucleus and the upper portion in the cuneate nucleus.

As discussed in chapter 14, lateral inhibitory synaptic interactions form the basis for sharpening the spatial resolution of skin sensory information (see Figs. 14.6, 14.7, and 14.8 on pages 327, 331, and 332, respectively). Because the axons of the dorsal columns are predominantly those of primary sensory neurons, the first opportunity for the lateral synaptic interactions required to establish center-surround receptive fields in this spinal projection pathway arises at the level of the dorsal column nuclei.

The ascending axons from the lateral sensory tract demonstrate a very different distribution of connections in the brainstem. The axons of the lateral tract originate from interneurons in the dorsal part of the spinal cord gray matter (see Fig. 15.5), and the inputs to these interneurons come principally from pain- and temperature-sensitive sensory neurons. Many of the ascending axons of the lateral sensory tract terminate in the reticular formation of the medulla, pons, and midbrain. In primitive organisms in which the forebrain is small or absent, the brainstem reticular system serves as the main center for integrating sensory and motor information, and the projection of the lateral sensory tract provides the information about temperature and pain required for coordinated motor responses to these stimuli. Thus, the sensory signals from the lateral sensory tract help modulate the motor systems of the spinal cord, via the descending reticulospinal connections described in chapter 11. In more complex brains (for example, in mammals), the reticular formation neurons that receive temperature and pain signals relay this information to higher brain centers, such as the thalamus (discussed later in this chapter). The reticular formation also sends widespread connections to the midbrain and forebrain, controlling the overall level of arousal and activity of the animal. Painful stimuli arouse the animal via these reticular formation connections.

In mammals, some of the ascending axons of the lateral sensory tract bypass the brainstem, instead passing directly from the spinal cord to the thalamus without any intervening synaptic connections. This direct projection stems from spinal cord interneurons that receive inputs from the fast-conducting pain-sensitive neurons (Aδ fibers; see Fig. 15.1). By contrast, the slow-conducting pain fibers (C-fibers) synapse onto the interneurons that project to the reticular formation via the lateral sensory tract. Thus, the fast-conducting pain system in the peripheral receptors is relayed most directly and rapidly to the thalamus, producing the fast, searing pain perception felt immediately upon injury. The slower-conducting C-fiber system underlies the prolonged burning sensation that accompanies an injury. This projection system of pain and temperature sensory pathways (Fig. 15.8) is called the **anterolateral system,**

Figure 15.8
The organization of the anterolateral system. Interneurons in the dorsal part of the spinal cord gray matter receive synapses from primary nociceptor neurons. The axons of the interneurons ascend in the contralateral sensory tract in the lateral columns. The pathway originating from the C-fibers connects diffusely to the reticular formation in the brainstem, while the pathway originating from the faster-conducting Aδ-fibers projects directly to the thalamus.


Cortex
Thalamus
Medulla and pons
Reticular formation
Lateral sensory tract
Interneurons
Fast pain receptors (Aδ-fibers)
Interneurons
Slow pain receptors (C-fibers)
Dorsal part of spinal cord gray matter

reflecting the position of the ascending axons in the lateral columns of the spinal cord. The anterolateral system also includes some tactile and proprioceptive information, although most of these mechanosensory projections reach the brain via the dorsal column pathway.

THE THALAMUS

As noted earlier, the anterolateral system carries pain and temperature information from the spinal cord to the thalamus, either directly or indirectly via the reticular formation. The thalamus is also the next relay stage for the tactile and proprioceptive information carried via the dorsal columns to the dorsal column nuclei in the brainstem. The neurons of the gracile and cuneate nuclei receive synapses from the ascending collateral branches of the primary sensory neurons. In turn, the axons of the dorsal nuclei interneurons exit ventrally, cross the midline, and form bilaterally symmetrical, large axon bundles near the ventral midline of the medulla (Fig. 15.9). These bundles, called the **medial lemniscus**, move progressively dorsally and laterally as they ascend through the midbrain. When the axons of the medial lemniscus reach the diencephalon, they enter the posterior portion of the ventral thalamus and make synapses on thalamic relay neurons.

As a result of the crossing (decussation) of the axons leaving the dorsal column nuclei in the medulla, the medial lemniscus on one side of the brain carries tactile and proprioceptive sensory information from the opposite side of the body. Thus, just as in the anterolateral system, the information reaching the thalamus on the right side of the brain in the dorsal column/medial lemniscus system comes from the left side of the body, and vice versa. In the anterolateral system, the crossover of axons occurs in the spinal cord; in the lemniscal system, the crossover occurs in the medulla. In both systems, decussation is accomplished by the axons of the first set of interneurons in the path—that is, those that receive synapses from the primary sensory neurons.

The lateral–medial somatotopic map observed in the dorsal column nuclei is evident in the ventral posterior thalamus as well. In the thalamus, however, the direction of the mapping is reversed. The tactile information from the hindlimbs projects to thalamic neurons in the most lateral portion of the ventral posterior thalamic nucleus, followed by information from the trunk and then the forelimbs as we move medially in the nucleus. This arrangement is illustrated in Figure 15.10. In the gracile and cuneate nuclei, on the other hand, the hindlimb sensory projection is the most medial, with forelimb information appearing in a more lateral position. In addition, in the ventral posterior thalamus, the most medial portion receives tactile inputs from the face, which enter the brain via the trigeminal cranial nerve (nerve V). Like the sensory inputs from the dorsal column nuclei, the trigeminal sensory information reaches the thalamus via the medial lemniscus.

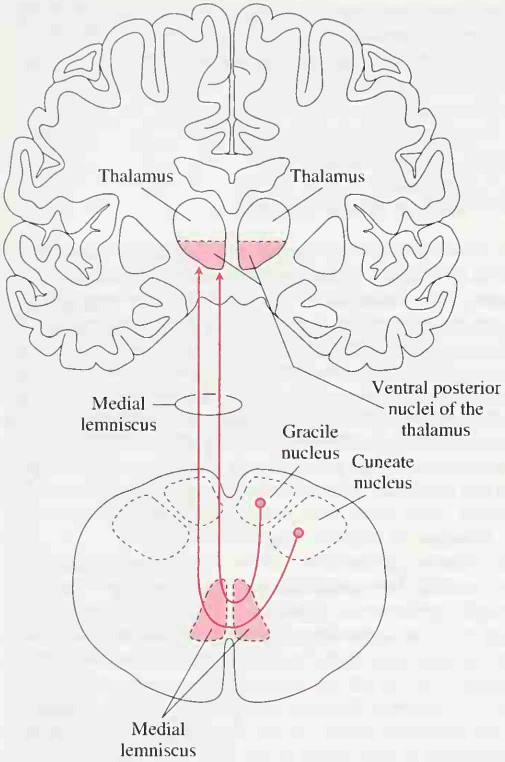
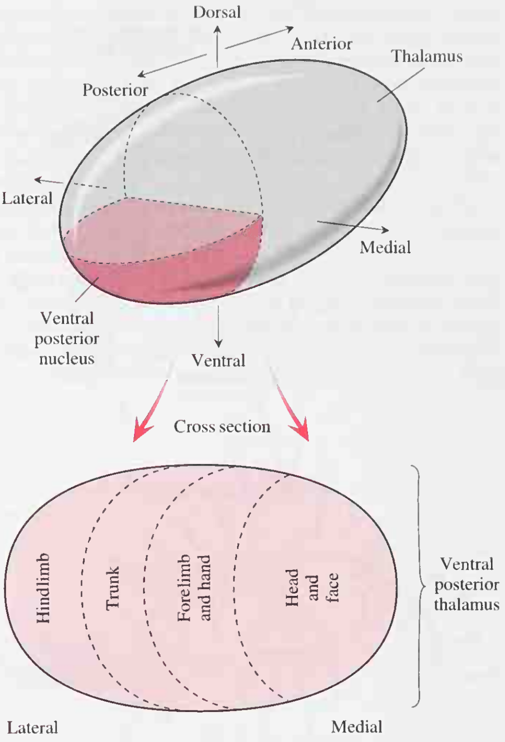


Figure 15.9
The projections from the dorsal column nuclei to the thalamus, in the diencephalon. The axons from the gracile and cuneate nuclei cross the midline and enter the medial lemniscus on the contralateral side of the medulla. This tract projects to the ipsilateral thalamus, where synaptic connections are made with neurons in the ventral posterior nucleus of the thalamus.

SOMATOSENSORY CORTEX

From the ventral posterior thalamus, the somatosensory information is relayed to the cortex. The main target in the cortex is the **postcentral gyrus** (Fig. 15.11), an outfolding located just behind the deep groove (the central sulcus) approximately at the anterior–posterior midpoint of the brain. Recall from chapter 11 that the primary motor cortex is located just in front of the central sulcus, in the precentral gyrus. Therefore, the primary motor area and the primary somatosensory area of the cortex parallel one another and are separated by only the central sulcus. The somatosensory cortex corresponds to Brodmann's areas 1, 2, and 3, while the primary motor cortex corresponds to Brodmann's area 4 (see chapter 11). Because of the decussation of the axons in the medial lemniscus in the medulla, the sensory cortex on the right

Figure 15.10
The somatotopic organization of the tactile sensory information in the ventral posterior thalamus.



side of the brain receives sensory information from the left side of the body, and vice versa. The same arrangement is found in the motor system, where the right motor cortex controls motor activity of the left half of the body.

The body surface is represented in a orderly way in the primary somatosensory cortex. Figure 15.11 shows that the sensory cortex contains a somatotopic map, like that found in the dorsal columns, the dorsal column nuclei, and the ventral posterior nucleus of the thalamus (Fig. 15.11). The sensory innervation of the toes, foot, and lower limb is represented at the most medial parts of the postcentral cortex, followed by the trunk and upper limb as we move progressively further from the midline along the postcentral gyrus. The face, lips, and tongue are represented in the most lateral portions of the primary somatosensory cortex.

The amount of somatosensory cortex devoted to a particular part of the body's surface does not correspond to the relative size of the body part.

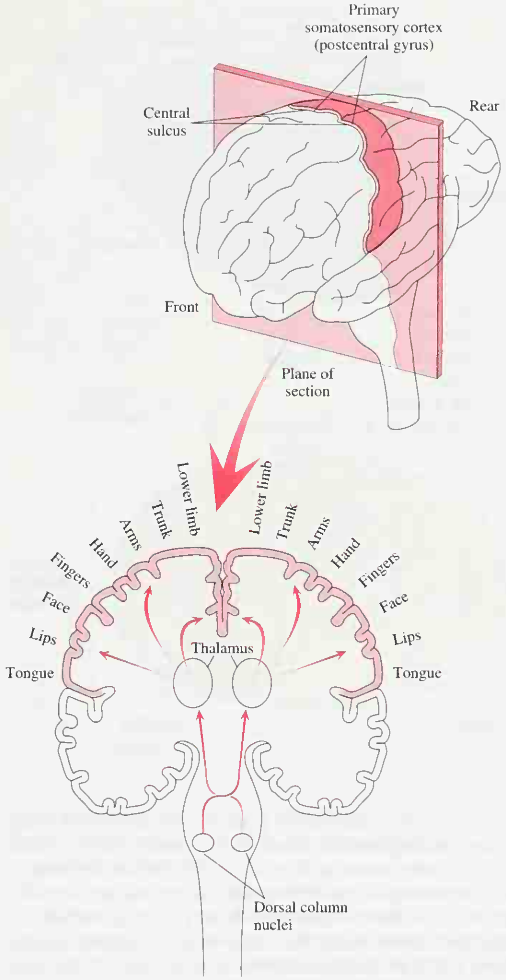
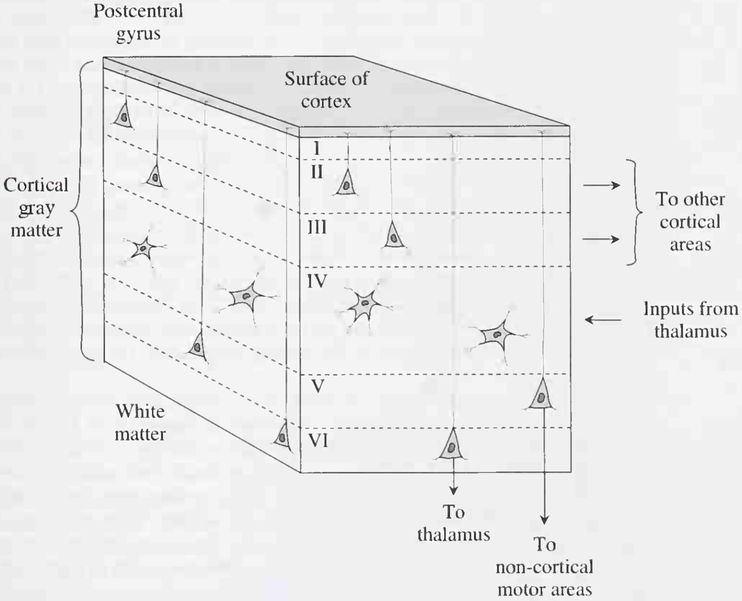


Figure 15.11
The somatotopic organization of somatosensory information in the primary somatosensory cortex, which is located just posterior to the central sulcus (upper diagram). The projections from the various parts of the body onto the somatosensory cortex are shown in the lower diagram, which depicts a section through the brain in the plane illustrated in the upper diagram. Because of the decussation of the ascending axons from the dorsal column nuclei in the brainstem, the sensory information on one side of the cortex comes from the contralateral side of the body.

Instead, it corresponds to the number of sensory neurons that innervate that region. In other words, the density of sensory innervation determines the size of the corresponding cortical representation. As we saw in chapter 14, human fingers are contacted by large numbers of touch-sensitive sensory neurons, each having a small receptive field, while the arm and trunk receive relatively few sensory neurons, each having a large receptive field. Consequently, in the somatosensory cortex of the human brain, the fingers have a large representation, while a relatively small area is devoted to sensory information from the arm and trunk. As noted in chapter 11, the same sort of organization is seen in the primary motor cortex. The lower limb is controlled by the most medial portion of the cortex, and the face and vocal apparatus are controlled by the most lateral portion. In addition, the amount of motor cortex devoted to a body part depends on the fineness and complexity of control required, rather than the size of the body part. In general, the amount of motor cortex closely corresponds to the amount of sensory cortex devoted to a particular body part.

Like other parts of the cortex, the somatosensory cortex is organized into six layers extending from the surface of the cortex to the underlying white matter. The basic cellular organization of these layers is described in chapter 11 (see Fig. 11.6 on page 243). As shown in Figure 15.12, the incoming axons from the ventral posterior thalamus make synaptic connections in layer

Figure 15.12
The somatosensory cortex is organized in layers. Inputs to the cortex and outputs to particular brain regions are located in specific layers of the cortex.



IV—the cortical layer dominated by stellate cells. The stellate cells are interneurons that make local synaptic connections with pyramidal neurons in other layers of the cortex. The sensory parts of the cortex, such as the primary somatosensory cortex, are targets for large numbers of axons that originate in the thalamus. Thus, layer IV is relatively thick in the sensory regions of cerebral cortex but comparatively thin in motor regions such as the primary motor cortex. The pyramidal neurons in layer VI of the somatosensory cortex send axons back to the thalamus, just as they do in layer VI of the motor cortex. This corticothalamic projection provides a feedback pathway by which the sensory cortex can influence the thalamic relay nucleus that supplies sensory information to the cortex.

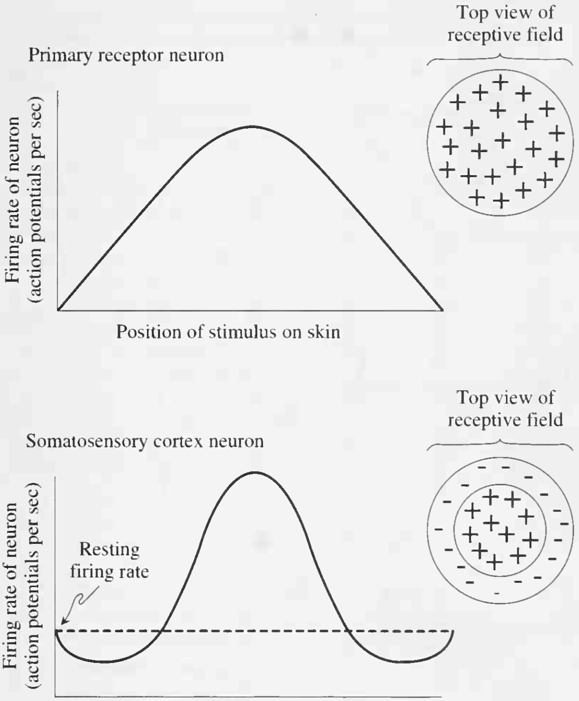
Sensory information is also required for proper motor function (see chapters 11 and 12). As a result, the somatosensory cortex sends outputs to motor regions of the brain. The large pyramidal neurons of layer V send axons to noncortical motor areas, including the basal ganglia. Connections to cortical motor areas are made by pyramidal neurons in layers II and III of the somatosensory cortex. The connections from the somatosensory cortex to cortical and non-cortical motor areas supply the motor system with necessary information about limb position and contact with the environment.

Receptive fields of cortical somatosensory neurons

How do the neurons in the somatosensory cortex respond to tactile stimulation of the skin? The primary receptor neurons are excited by mechanical stimulation applied to their receptive fields in the skin. As discussed in chapter 14, lateral inhibitory interactions mediated by interneurons alter the receptive-field properties of the neurons receiving synaptic input from the primary receptors. In the touch system, these lateral interactions occur at all synaptic relay stations: in the dorsal column nuclei, in the thalamus, and in the cortex itself. Because of lateral inhibition, the receptive fields of second-order and higher sensory neurons have the center-surround organization described in chapter 14. Many cortical neurons also possess this type of receptive field, in which tactile stimulation in the center of the field excites the neuron and stimulation applied to the surrounding region inhibits it. Figure 15.13 shows the response of a neuron in the somatosensory cortex to a touch stimulus applied at various positions on the skin and provides an overview of the receptive field. The lateral inhibitory interactions increase the brain's ability to distinguish two points of stimulation from one, thereby increasing the spatial resolution of the sensory system (see, for example, Fig. 14.6 on page 327).

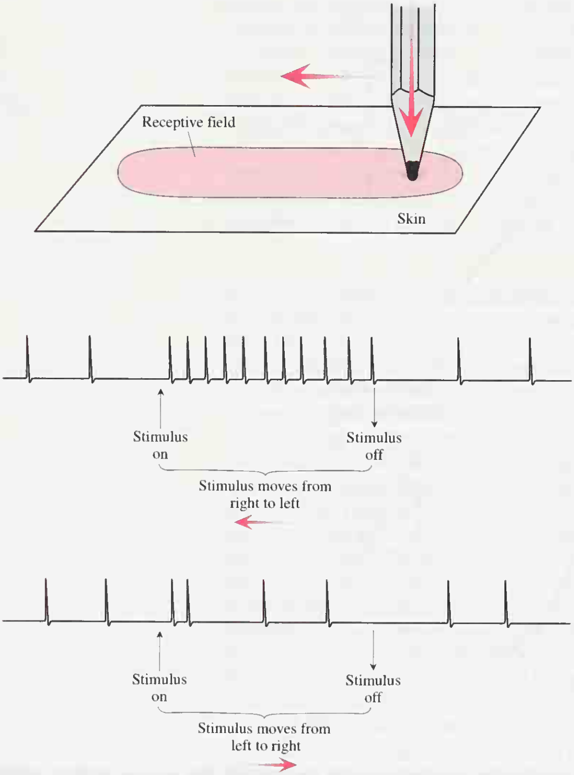
In addition, cortical neurons can have more complicated types of receptive fields. For example, in the neuron illustrated in Figure 15.14, the receptive field is long and narrow, rather than circular or oblong. A touch applied to a single location within the receptive field produces little effect. In contrast, a stimulus brushed along the receptive field, moving from right to left, produces a sustained increase in action potential activity. Thus, this type of cortical neuron prefers a moving stimulus to a stationary stimulus. If we reverse the direction of the stimulus so that it moves from left to right, little response is observed. Not only must the stimulus be moving, but it must also

Figure 15.13
The receptive fields of neurons in the somatosensory cortex differ from the receptive fields of primary sensory neurons. The upper diagram shows the rate of firing action potentials in the primary sensory neuron in response to a touch stimulus applied to various positions along the surface of the skin. A top view of the receptive field is also shown. The lower diagram shows the comparable behavior for a cortical neuron and a top view of the center-surround receptive field observed for some cortical neurons.



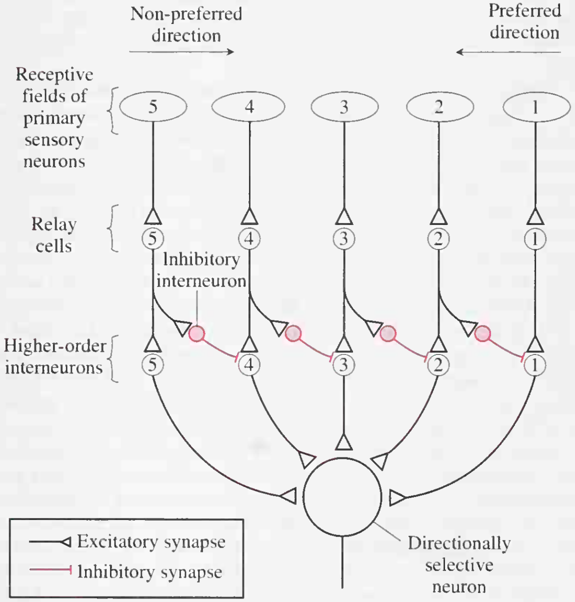
move in a particular direction. Other neurons in the somatosensory cortex would demonstrate the opposite direction preference, and still others would have different orientation preference. Within the population of cells in the somatosensory cortex, all orientations of direction preference for moving stimuli covering all points of the compass would be represented. Complex receptive fields like that illustrated in Figure 15.14 could arise from relatively simple combinations of synaptic connections from lower-level neurons in

Figure 15.14
The response of a directionally selective cortical neuron. The receptive field on the skin is an elongated strip of skin. When a touch stimulus is applied to the skin and moved across the receptive field, the neuronal response depends on the direction of movement. In this case, a stimulus moving from right to left produces a large increase in firing of the cortical neuron. A stimulus moving from left to right produces only a weak response.


Receptive field
Skin
Stimulus on
Stimulus off
Stimulus moves from right to left
Stimulus on
Stimulus off
Stimulus moves from left to right

the sensory pathway. For example, the circuitry shown in Figure 15.15 could produce directional selectivity for moving stimuli. In a simple variation on the general lateral inhibitory scheme, inhibitory interneurons send connections to only one side. Let us examine how this arrangement gives rise to directional selectivity.

Figure 15.15
Hypothetical synaptic circuitry that could produce a directionally sensitive response in a cortical somatosensory neuron. The circuit begins with five primary sensory neurons with receptive fields arrayed linearly along the skin (top level). These primary sensory neurons make excitatory synaptic connections onto a group of relay cells (second level). The relay cells excite higher-order interneurons (third level), whose outputs converge on a cortical neuron. The relay cells also excite inhibitory interneurons (red) that make inhibitory synapses onto the higher-order neurons of the neighboring pathway, but only to one side. (See the text for a description of how this arrangement produces a directionally selective response in the cortical neuron.)



Consider a stimulus moving across the receptive fields of the primary sensory neurons on the skin surface in the preferred direction, from right to left. This stimulus first encounters the receptive field of primary neuron 1, which responds by firing a burst of action potentials. This burst of activity in turn excites relay cell 1 and higher-order interneuron 1. The higher-order interneuron ultimately makes an excitatory connection with the directionally selective cortical neuron, and the burst of action potentials in the interneuron causes the first one or two action potentials in the cortical neuron shown in Figure 15.14. As the stimulus continues to move along the skin, it leaves the receptive field of primary neuron 1, and the activity in this branch of the path leading to the cortex ceases.

As it leaves the first receptive field, the stimulus moves into the receptive field of primary neuron 2. There, it stimulates a burst of action potentials in primary sensory neuron 2, which are relayed to the directionally selective cortical neuron in a manner analogous to that described for the pathway from the first sensory neuron. This activity in the pathway of primary neuron 2 has two effects. First, it excites the directionally selective cortical neuron, producing the next one or two action potentials during the stimulus (see Fig. 15.14). Second, action potentials in relay cell number 2 excite a lateral inhibitory interneuron that inhibits the higher-order interneuron in pathway number 1. Because the activity in that pathway has already ceased, however, the inhibition has no functional effect on the relay of information.

As the stimulus continues to move, it successively encounters the receptive fields of primary sensory neurons 3, 4, and 5, each of which relays excitation to the directionally selective cortical neuron. Thus, the excitation that produces the burst of action potentials in the cortical neuron is sustained as the stimulus moves from right to left, producing the prolonged burst of activity observed during the moving stimulus (see Fig. 15.14).

Now consider what happens when the stimulus moves from left to right—a movement opposite to the preferred direction. The stimulus first encounters the receptive field of primary sensory neuron 5, which is excited by the stimulus. The burst of action potentials is relayed to the directionally selective cortical neuron, producing one or two action potentials at the onset of the stimulus. The activity in this pathway is also relayed to the higher-order interneuron in the neighboring pathway (number 4) via the lateral inhibitory interneuron. The stimulus next enters the receptive field of primary sensory neuron 4, and the excitation is passed from the primary sensory neuron to relay cell number 4. When the excitation from the relay cell reaches the higher-order interneuron in pathway 4, however, it must sum with the preexisting inhibition resulting from the activation of the inhibitory interneuron of pathway 5. The higher-order interneuron of pathway 4 is pre-inhibited, rendering it less likely to fire when the receptive field of primary sensory neuron 4 is stimulated. If the inhibition is sufficiently strong and long-lasting, then it may completely prevent higher-order neuron 4 from firing. In such a case, the directionally selective cortical neuron will receive no excitation and will cease firing.

The activation of the relay cell in pathway 4 excites the lateral inhibitory interneuron of that pathway, feeding inhibition to the higher-order interneuron of pathway 3. That interneuron is then pre-inhibited when excitation arrives from the stimulation of receptive field 3 by the moving stimulus. Because of the lateral inhibition, the directionally selective cortical neuron is less likely to be stimulated when the stimulus moves from left to right. The result is the weak response of the cortical cell to movement in the nonpreferred direction, shown in Figure 15.14.

The circuit shown in Figure 15.15 provides a simple example of how synaptic interconnections can give rise to individual neurons that extract particular information about the environment. In general, receptive fields of cortical neurons are more complex than those of lower-order neurons in the sensory pathways. Because of the elaborate interconnections among the neurons of the cerebral cortex, ample opportunity exists for neural circuits that are tuned to detect complex combinations of sensory events.

SUMMARY

The somatic senses provide information about the interaction of the skin with the environment and about the positions of joints and muscles. The skin contains several types of sensory receptor structure, each specialized for the reception of a particular type of sensory information. Each sensory modality (such as touch, pressure, and pain) is mediated via a specific class of sensory receptor. Receptors that are sensitive to touch or pressure are called mechanoreceptors. Some mechanoreceptors consist of nerve endings encapsulated within fibrous capsules called corpuscles. In human skin, such mechanoreceptors include the Pacinian corpuscle, the Meissner corpuscle, and the Ruffini corpuscle. Other mechanoreceptors are the Merkel disks and the hair follicle receptors. The mechanoreceptors can also be distinguished by their adaptation properties, with some adapting rapidly and others slowly during a sustained mechanical stimulus. The skin also contains thermoreceptors that are stimulated by cooling the skin below normal body temperature (cold receptors) or warming the skin above the normal body temperature (warm receptors). Nociceptors are another class of receptor activated by stimuli that injure the skin (such as burns or punctures).

Joint position, muscle length, and muscle tension—a type of sensory information called proprioception—are also signaled within the somatosensory system. Muscle length is encoded by the sensory neurons that innervate the muscle spindles. Muscle tension is signaled by the Golgi tendon organs. Information about the angle of the joint is provided by joint receptors, which are sensory neurons that innervate the joint capsule.

The sensory receptors can also be classified according to the conduction velocity of their axons in the peripheral nerves. The fastest-conducting axons are those of the muscle spindles (group Ia), followed closely by the Golgi tendon organ axons (group Ib). These fast-conducting group I axons are also known as group Aα. The mechanoreceptors of the skin are innervated by sensory neurons with medium-size, myelinated axons (group II; also known as group Aβ) that conduct more slowly than the muscle receptors. The joint receptor neurons also have axons that conduct in group II. The smallest-diameter myelinated axons (group III; also known as group Aδ) are those of the cold receptors and the rapid, searing-pain nociceptors. Group IV is the slowest-conducting group of axons in peripheral nerves (also called group C, or C-fibers). Group IV includes the axons of the warm receptors and of the nociceptors that underlie the sensation of slow, burning pain.

In the spinal cord, somatosensory information is carried to the brain by ascending axons found in the dorsal columns, lateral sensory tract, and spinocerebellar tract. The dorsal column projection, which consists of collaterals of the axons of primary sensory neurons, carries primarily information from mechanoreceptors and proprioceptors. The lateral sensory tract consists of axons of interneurons in the spinal-cord gray matter that receive synaptic inputs from thermoreceptors and nociceptors, plus some mechanoreceptors and proprioceptors. The spinocerebellar tract, which is also located in the lateral columns of the spinal-cord white matter, carries somatosensory information to the cerebellum. The dorsal column axons project to the brainstem, where they terminate in the two dorsal column nuclei, the gracile nucleus and the cuneate nucleus. The axons of the lateral sensory tract project to the reticular formation of the brainstem and (in some species) directly to the thalamus.

A major target of the ascending somatosensory information is the thalamus. The dorsal column nuclei project to the thalamus via the medial lemniscus, which crosses the midline in the medulla and projects to the contralateral thalamus. The axons of the lateral sensory tract cross the midline in the spinal cord and also project to the contralateral brain. Thus, sensory information from the left side of the body is sent to the thalamus on the right side of the brain. The neurons of the thalamus relay the somatosensory information to motor control areas of the brain and to the somatosensory cortex, which is located in the postcentral gyrus. At each relay nucleus, including the thalamus, lateral interactions mediated by local interneurons modify and sharpen the receptive field properties of the neurons, giving rise to center-surround receptive fields and increasingly complex kinds of receptive fields. In the somatosensory cortex, for example, some neurons respond to only complex types of sensory stimulation, such as an object moving across the skin in a particular location in a particular direction. Neurons with such complex response requirements are well suited to extract information about patterns of sensory stimulation.

16

The Visual System: Retina

Each species has a dominant sensory system that it uses preferentially to gather information from the environment. For humans, the sense of vision is a dominant sense, playing a central role in our interaction with the environment. Unlike the mechanoreceptors and the somatosensory pathways described in chapter 15, visual sensory receptors allow us to gather information about the environment from afar, without having to come into direct contact with the object giving rise to the sensation. In this chapter, we will consider this important sensory system. We will begin by examining in some detail the sensory organ of vision, the eye, paying special attention to the neural part of the eye, the retina. In chapter 17, we will consider how the visual parts of the brain analyze and modify the information passed on from the eye to form a representation of objects and their relationships in the visual world.

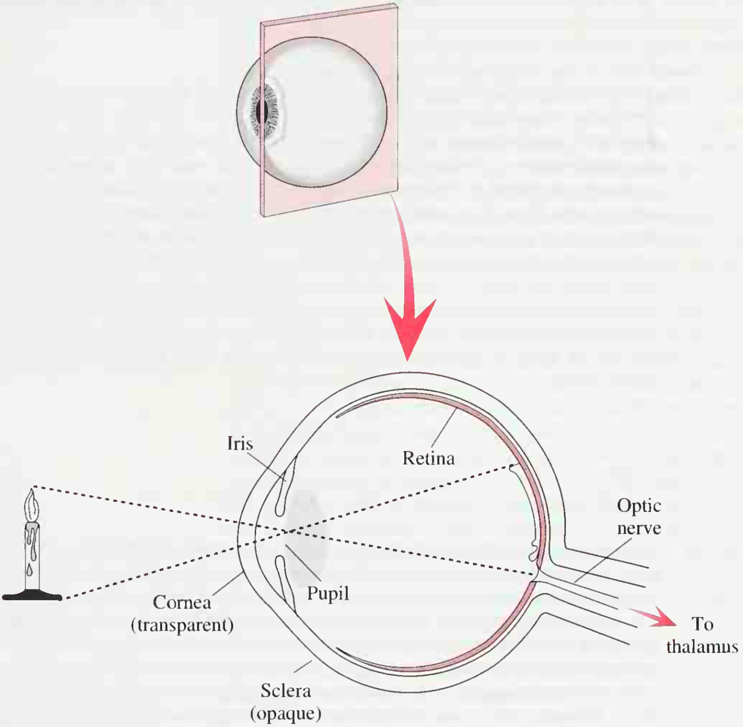
STRUCTURE OF THE VERTEBRATE EYE

Light-sensitive sense organs are found in a wide variety of organisms. Indeed, even single-celled organisms possess light-sensing organelles (in addition to the light-gathering photosynthetic organelles found in bacteria and plants). For example, single-celled algae have a light-sensitive "eye-spot" that is used to sense the direction of illumination, providing information that allows the organism to exhibit positive phototaxis. A somewhat more complex example of a photosensitive organ in multicellular organisms is the eye-spot of the flatworm *Planaria,* which also provides sensory information enabling phototaxic behavior (in this case, negative phototaxis). Beyond these simple light-gathering organs, a variety of animals in both the invertebrate and the vertebrate worlds—including humans—have developed more complicated light-sensing organs that are able not only to gather light but also to optically focus the light onto the sensory surface of the organ to form an image of the outside world.

Figure 16.1 provides a diagram showing a schematic cross section of a human eye. Light enters the eye through the transparent covering at the front of the eye, the **cornea.** It then passes into the posterior portion of the eye through an aperture, the **pupil,** whose diameter is controlled by the muscles of the colored part of the front of the eye, the **iris.** Behind the iris lies the lens, which focuses the incoming light on the back of the eye. (The cornea also helps focus the light, because of its curvature.)

As we saw in chapter 14, the primary job of any sensory organ is to convert the energy form of the sensory stimulus into an electrical signal that

Figure 16.1
The structure of the human eye. The retina is shown in red at the rear of the inside of the eye.



can be transmitted and analyzed by the cells of the nervous system. In the eye, this sensory transduction process is accomplished in the neural part of the eye—that is, the retina at the back of the eye (shown in red in Figure 16.1). Because the sensory stimulus consists of photons of light in the case of the eye, this process is called **phototransduction**, and it is carried out in the light-sensitive neurons of the retina, the **photoreceptors**. The organization of a typical vertebrate retina is shown in Figure 16.2. The photoreceptors are actually found at the rearmost part of the eye, facing the back of the eye. To reach the cells that absorb the light and translate it into electrical signals, the light must first traverse all the other cells of the retina.

Including the photoreceptors, five general classes of neuron make up the retina. The photoreceptors make synaptic connections with second-order

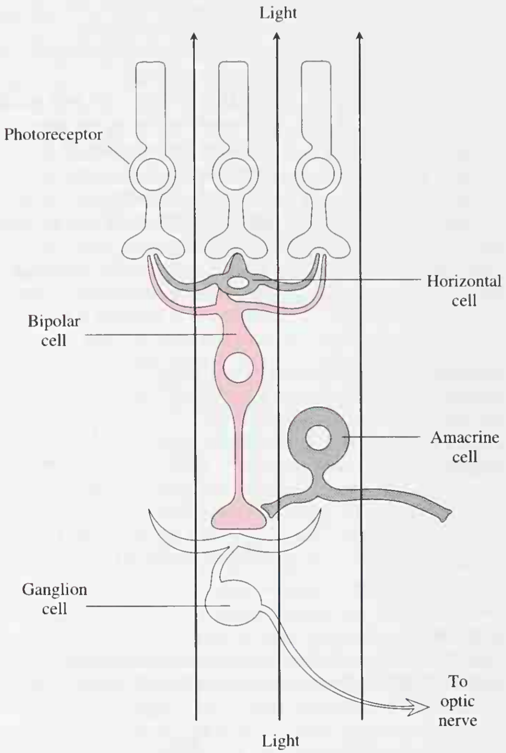


Figure 16.2
The neurons of the retina. The photoreceptors are located at the rear of the retina and make synaptic connections with horizontal cells and bipolar cells. The bipolar cells then connect with the amacrine cells and ganglion cells in the inner portion of the retina. The axons of the ganglion cells make up the optic nerve.

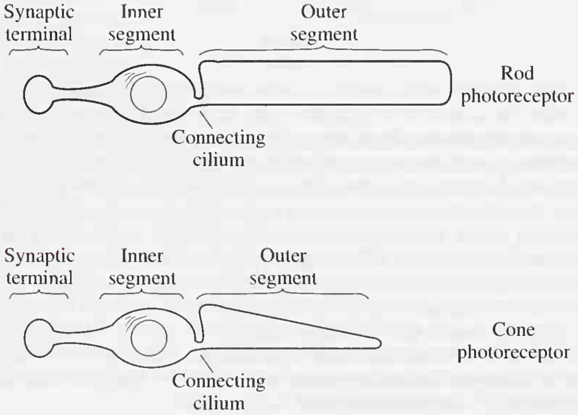
neurons called **bipolar cells**, which in turn make synapses onto retinal **ganglion cells**. The axons of the ganglion cells form the optic nerve, which carries the visual information from the eye to the thalamus in the diencephalon. In addition to this through-conducting pathway, two types of lateral interneurons are found in the retina. The **horizontal cells** receive synaptic inputs from the photoreceptors and then make synaptic connections with bipolar neurons or (in some species) onto the synaptic terminals of the photoreceptors. The **amacrine cells** receive inputs from the bipolar cells and make synaptic connections back onto bipolar cell synaptic terminals and onto the dendrites of ganglion cells. For both horizontal cells and amacrine cells, one synaptic target of the lateral interneuron can be the synaptic terminal of the cell that feeds the lateral interneuron. This type of feedback synapse, in which a cell makes a synapse back onto the synaptic terminal that is presynaptic to it, is quite common in the retina.

The Light Response of the Photoreceptors

In this section, we will examine the sensory transduction process in the photoreceptors to see how the electromagnetic energy of light is converted into an electrical signal in the photoreceptor. Most vertebrate retinas include two classes of photoreceptors: **rods** and **cones.** The structural organization of these photoreceptors is shown in Figure 16.3. The light-sensitive portion of the cell, where light is absorbed and phototransduction occurs, is called the **outer segment.** In rods, the outer segment is long and cylindrical (rod-shaped—hence the name); in cones, the outer segment is typically tapered toward the distal end (cone-shaped). In vertebrate photoreceptors, the outer segment is actually a highly modified cilium, shaped by evolution to carry out the light-sensing function of the cell. The outer segment is connected to the rest of the photoreceptor cell via a thin ciliary neck that contains a vestigial ciliary apparatus. The non–light-sensitive part of the cell, which contains the nucleus and the usual cellular machinery of neurons, is called the **inner segment** (see Fig. 16.3). At the other end of the photoreceptor inner segment is the **synaptic terminal** of the photoreceptor, where synaptic connections are made with the second-order horizontal and bipolar neurons of the retina.

From the point of view of electrical signaling, an important functional characteristic of the photoreceptors is their spatial compactness. Recall from

Figure 16.3
The structural organization of rod photoreceptors (top) and cone photoreceptors (bottom). The outer segment is the light-sensitive portion of the photoreceptor.



chapter 4 that electrical current injected at a point in an axon cannot spread very far along the nerve fiber before it leaks out across the cell membrane. Consequently, the nervous system needs action potentials to transmit electrical signals across long distances. The total length of the photoreceptor (<100 μm) is so short, however, that a change in membrane current at the tip of the outer segment can easily spread to the other end of the cell, producing a change in membrane voltage at the synaptic terminal purely by passive electrical spread of the injected charge along the cell interior. Thus, short neurons like photoreceptors do not require action potentials to carry information to the synaptic terminal. Indeed, the photoreceptors do not have voltage-dependent sodium channels and do not generate action potentials. Instead, the generator potential produced by the phototransduction process in the outer segment spreads through all parts of the cell, including the synaptic terminal.

The electrical response of the photoreceptors to light

We will now examine the electrical signal produced in the photoreceptor by the absorption of light in the outer segment. If we record the membrane potential of a vertebrate photoreceptor cell in darkness, we find that the resting membrane potential is unusually positive for a neuron, with a value of -30 to -40 mV being typical (Fig. 16.4). If we then turn on a bright light, the membrane potential of the photoreceptor shifts to near -70 mV (see Fig. 16.4). In the light, the membrane potential resembles that of typical neurons; in darkness, however, the photoreceptor is depolarized. Thus, the response to light (the receptor potential of the photoreceptor) is a hyperpolarization. If we use a dim light instead of a bright light, a smaller hyperpolarization results (see Fig. 16.4). Applying light of various intensities, we would find that the degree of hyperpolarization depends on light intensity, with brighter lights producing a more negative membrane potential than dimmer lights. The relationship between light intensity and membrane potential is summarized in Figure 16.5. Like other receptor potentials described in chapter 14, the receptor potential of the photoreceptor is a graded potential, with an amplitude that depends on the magnitude of the sensory stimulus. Unlike other sensory receptors, however, the receptor potential of the photoreceptor is a hyperpolarization, rather than a depolarization. (You might picture the "stimulus" for the photoreceptor as being *darkness*, so that illumination acts by *removing* the "stimulus.")

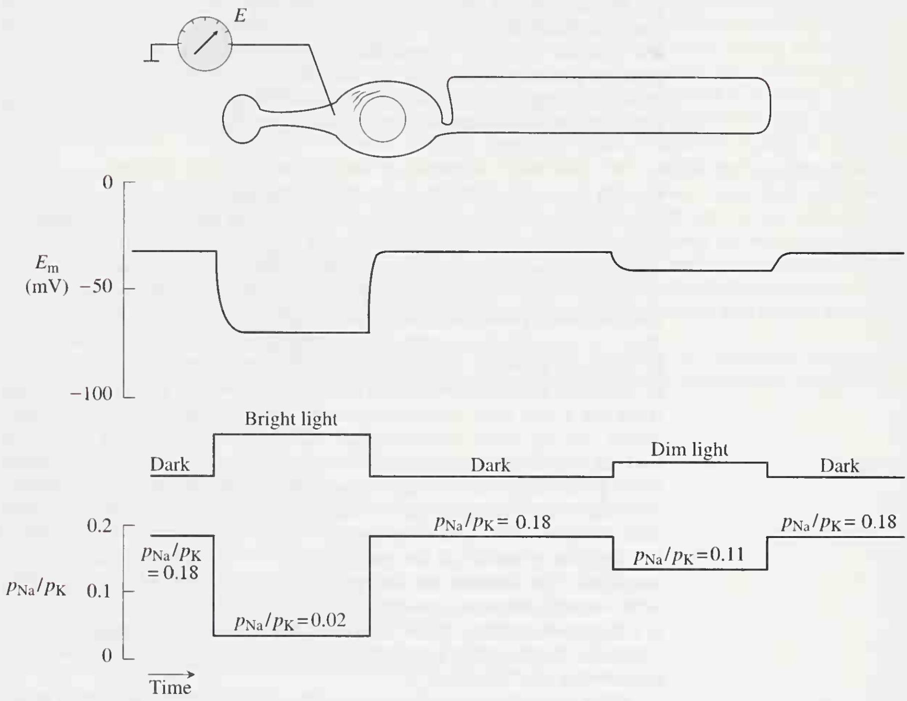
What kind of ionic mechanism would you expect to underlie the changes in membrane potential of the photoreceptor cell upon illumination? In chapter 4, we showed that the resting membrane potential of a neuron is governed by the permeability of the membrane to sodium and potassium ions, p_{Na} and p_{K}. For a given set of ionic conditions, the membrane potential can be calculated from the Goldman equation:

$$E_{\mathrm{m}} = 58\ \mathrm{mV}\log\left(\frac{[\mathrm{K}^+]_{\mathrm{o}} + b\,[\mathrm{Na}^+]_{\mathrm{o}}}{[\mathrm{K}^+]_{\mathrm{i}} + b\,[\mathrm{Na}^+]_{\mathrm{i}}}\right) \qquad (16.1)$$

where the scaling factor b is $p_{\mathrm{Na}}/p_{\mathrm{K}}$. As we have seen, the usual resting value of b in a neuron is approximately 0.02, with p_{K} about 50 times greater than

Figure 16.4

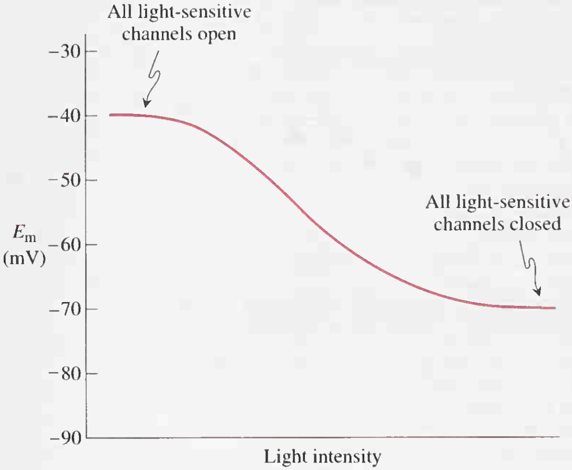
The effect of light on the membrane potential of the photoreceptor. In darkness, the relative sodium permeability is high and the cell is depolarized. Light reduces the sodium permeability and makes the membrane potential more negative.



p_{Na}. The resting potential is near −70 mV under the usual ionic conditions (see chapters 3 and 4). If the ratio p_{Na}/p_K were 0.18 instead of 0.02, however, the Goldman equation indicates that the resting potential would be near −40 mV, which is the approximate membrane potential of the photoreceptor in darkness. Thus, a shift of p_{Na}/p_K from 0.18 to 0.02 could account for the shift in membrane potential of the photoreceptor observed when going from darkness to bright light.

Figure 16.4 shows the changes in p_{Na}/p_K associated with changes in membrane potential of the photoreceptor. The altered ratio results from a

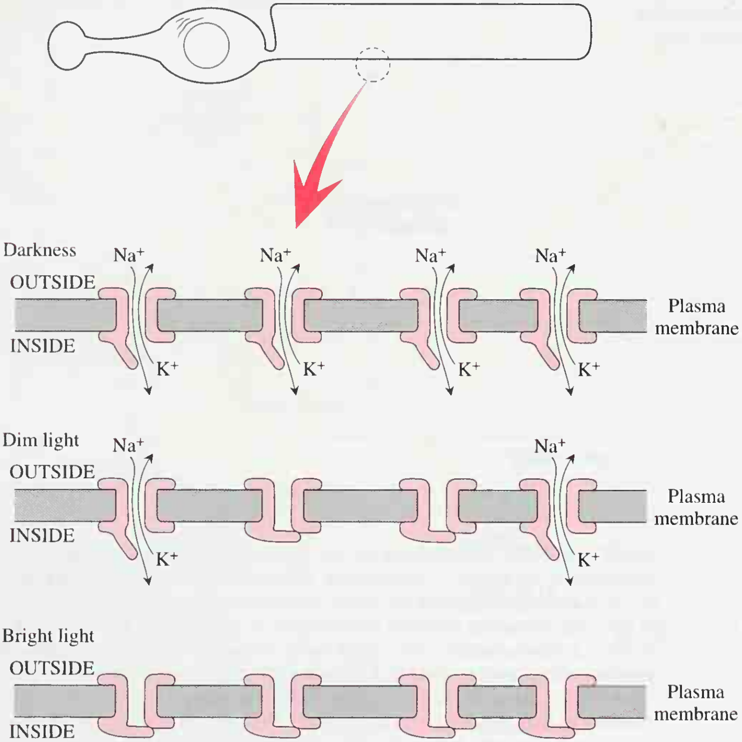
Figure 16.5
The relationship between light intensity and membrane potential in a photoreceptor.



reduction in ionic permeability of the photoreceptor outer segment upon illumination. In darkness, nonspecific cation channels in the plasma membrane of the outer segment are open. As we saw with synaptic transmission at the neuromuscular junction (see chapter 7), nonspecific cation channels produce a depolarization when they open. Thus, the open cation channels maintain the photoreceptor in a depolarized state in darkness. Light closes these cation channels, and the fraction of channels closed depends on the intensity of the light. Figure 16.6 illustrates the effect of light on the channels of the outer segment. When the light is sufficiently bright to close all of the channels, the membrane potential reaches its most negative value, and further increases in light intensity fail to produce any further change in membrane potential (see Fig. 16.5).

We now turn our attention to the linkage between absorption of light in the outer segment and the closure of the nonspecific cation channels. This linkage has two aspects. First, the presence of the light must be detected, which requires a detector molecule that absorbs light. Second, the detector molecule must then generate a cellular signal that ultimately leads to the closing of the ion channels and thus to hyperpolarization of the photoreceptor cell. In the next section, we will discuss the properties of the detector molecule. We will then describe the cellular signaling system that is triggered by the absorption of light by the detector molecule.

Figure 16.6
Light closes nonspecific cation channels in the plasma membrane of the photoreceptor outer segment. The percentage of channels closed depends on the light intensity.



The light-absorbing molecules in the photoreceptor outer segment

To detect the presence of light, some type of molecule within the photoreceptor must absorb a photon of light and then signal this event to the cell. That job is carried out by the **visual pigment molecules**, membrane proteins that are present at high density in the outer segment. To increase the chances that light will be absorbed as it moves through the outer segment, the membranes containing the pigment molecules are arranged in multiple layers perpendicular to the long axis of the outer segment (Fig. 16.7). In the rods, the pigment molecules are located in the membranes of intracellular

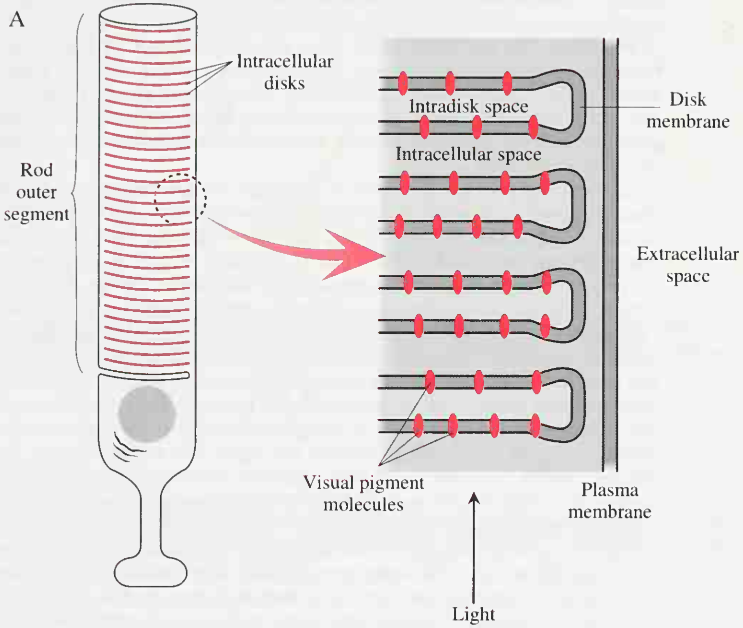
disks, whose membranes are not continuous with the plasma membrane of the outer segment. These intracellular disks are arranged in a tightly packed stack along the outer segment, like a stack of dimes inside a test tube (see Fig. 16.7A). A similar arrangement is seen in the cones, although the stack of membrane is formed by infoldings of the plasma membrane (see Fig. 16.7B). In both cases, the functional effect is the same: a photon of light must pass through a series of approximately 2000 membranes, each studded with a high density of light-absorbing molecules, in order to propagate from one end of the outer segment to the other without being absorbed. As a result, photons reaching the outer segment will usually be absorbed and detected by the photoreceptor.

Each type of photoreceptor has its own type of visual pigment molecule. Humans have four types of photoreceptors (three types of cones and one type of rod) and thus four classes of visual pigment molecules. Each of the four classes absorbs light in the visible part of the electromagnetic spectrum, in the range of wavelengths from approximately 400 nm to 700 nm. Each class is maximally sensitive to light in a different range of wavelength, however.

The best-studied type of visual pigment molecule is **rhodopsin**, which is found in rod photoreceptors. Our discussions of visual pigment molecules will focus on rhodopsin, because most of what we know about these membrane proteins stems from studies of this rod pigment. Each pigment molecule is formed by a combination of a large protein molecule—**opsin**—with a special molecule that actually absorbs the light—the **chromophore.** The chromophore is the same for all visual pigment molecules: the aldehyde of vitamin A_1, which is called **retinal** (the "-al" is pronounced like the "Al-" in "Albert," because it comes from the word "aldehyde"). Therefore, the different light-absorbing properties of the four classes of pigment molecules must arise from differences in the opsin proteins made in the rods and in the three cone types. Interestingly, both retinal by itself and opsin protein by itself are colorless—that is, neither absorbs light in the visible wavelengths (both opsin and retinal absorb light in the ultraviolet region, at wavelengths shorter than those the human eye can sense). When retinal is chemically attached to opsin, however, the wavelength that can be absorbed shifts toward longer wavelengths, moving the absorption into the visible region. The amount of the shift, and thus the sensitivity to different parts of the visible spectrum, depends on the properties of the opsin protein. Because each class of pigment molecule has its own type of opsin, each class absorbs light differently.

The structure of the light-absorbing chromophore group, retinal, is shown in Figure 16.8. Retinal consists of a carbon ring structure with a long chain of carbon atoms sticking off to the side. The point of attachment to the opsin protein is at the end of carbon chain, where the oxygen atom is attached via an aldehyde linkage. Retinal can assume two biologically important alternative shapes (called **isomers**). The chain of carbon atoms can be either straight (**all-*trans* retinal**) or bent by a rotation around the double bond between carbon atoms 11 and 12 in the molecule (**11-*cis* retinal**). The biological importance of these shapes derives from the fact that retinal is in the 11-*cis* conformation in darkness, but undergoes a conformational change to the all-*trans* isomer when it absorbs a photon

Figure 16.7
(A) The location of visual pigment molecules in rod photoreceptors.



of light. This **photoisomerization** of 11-*cis* retinal to all-*trans* retinal upon absorption of a photon is the only light-dependent process in all of vision, and it forms the basis of the sense of sight.

Each visual pigment molecule includes a single retinal chromophore group attached via a covalent chemical bond to a particular amino acid in the opsin protein. The protein folds to form a pocket in which the folded, 11-*cis* isomer of retinal fits snugly. Figure 16.9 shows this structure for the rhodopsin molecule. Opsin is a membrane protein that snakes its way through the membrane a total of seven times. The seven transmembrane segments are arranged in a circle (see Fig. 16.9), with parts of several individual segments in close proximity to the 11-*cis* retinal, which is chemically linked to the seventh segment. When the chromophore absorbs a photon, it straightens to become the all-*trans* isomer. This action alters the position of the chromophore in its protein pocket, which in turn induces a conformation change in the opsin (see Fig. 16.9). When the transmembrane segments shift position with respect to each other, the cytoplasmic

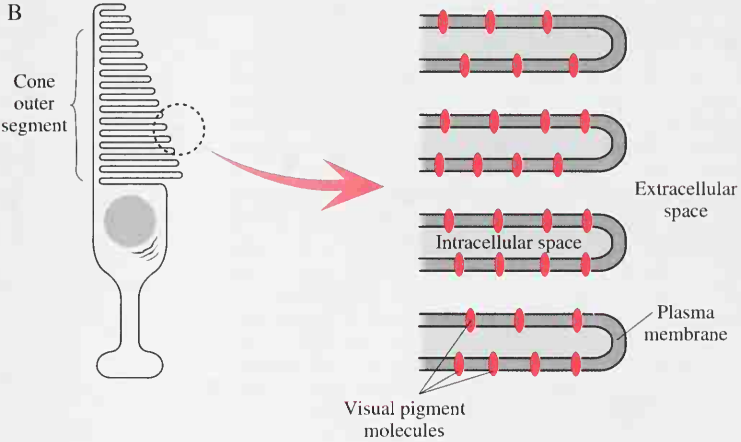


Figure 16.7 (continued)
(B) The location of the visual pigment molecules in cone photoreceptors.

tail of the molecule changes conformation as well, revealing reactive sites at which the photoactivated rhodopsin can interact with other proteins in the outer segment. These interactions form the basis of the signal that ultimately culminates in the closing of the nonspecific cation channels, which produces the hyperpolarizing light response of the photoreceptor.

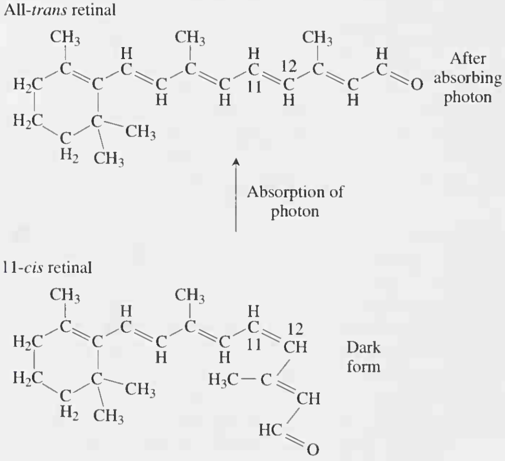
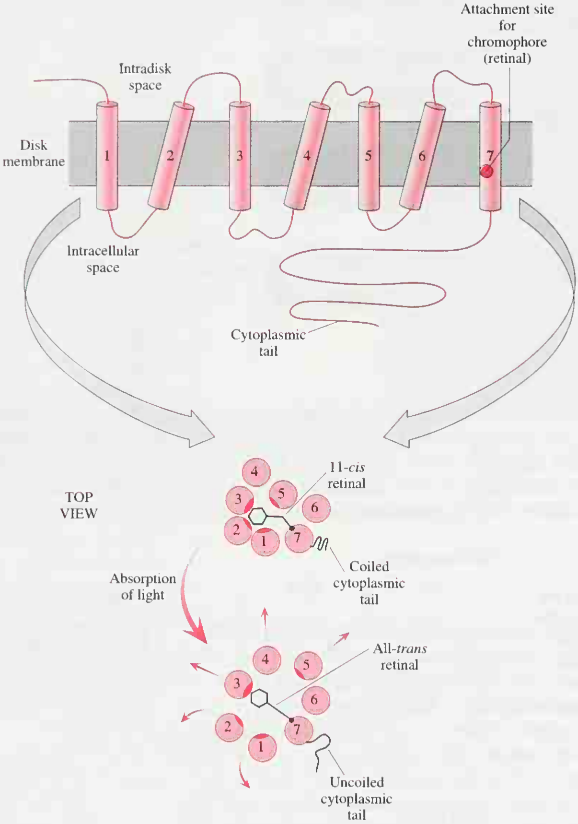


Figure 16.8
The structure of the chromophore group of visual pigment molecules. The chromophore is the aldehyde of vitamin A. In the dark, the chromophore is in a folded configuration (11-*cis* retinal). Upon absorption of a photon, the chromophore straightens to the all-*trans* isomer.

Figure 16.9
The structure of the visual pigment molecule rhodopsin. The molecule threads through the membrane seven times. When the 11-*cis* retinal chromophore group absorbs a photon and isomerizes to the all-*trans* form, a conformational change is induced in the opsin protein.



This linkage between photoactivated rhodopsin and membrane conductance is discussed in the next section.

Rhodopsin activates G-proteins

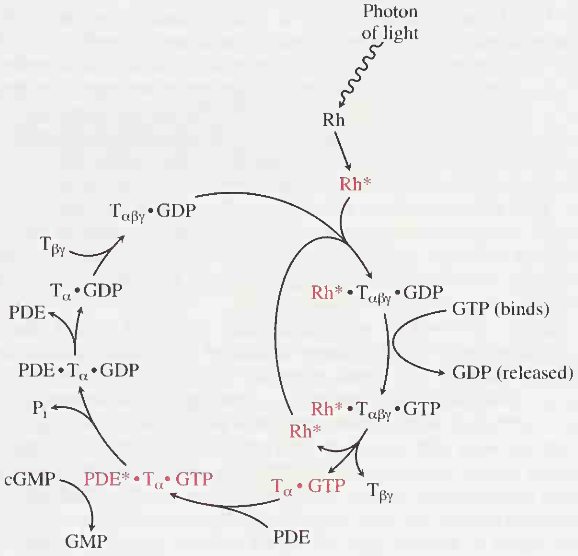
In our description of synaptic transmission (see chapter 8), we introduced the family of neurotransmitter receptors that act via GTP-binding proteins (G-proteins). When neurotransmitter binds to the receptor, the receptor becomes capable of interacting with and activating G-proteins by catalyzing the binding of GTP to the G-protein. The G-proteins then carry out the changes in cellular properties induced by the neurotransmitter.

Rhodopsin is actually a member of the family of G-protein–coupled neurotransmitter receptors. Structurally, all members of this family resemble rhodopsin, including seven transmembrane segments and a pronounced cytoplasmic loop at the end of the molecule. This cytoplasmic loop is the site at which the activated receptor interacts with intracellular G-proteins. When rhodopsin is activated by absorption of a photon of light, the conformation change reveals a binding site for G-proteins in the cytoplasmic tail, allowing rhodopsin to set in motion the next event in the signaling cascade of phototransduction. In essence, rhodopsin acts as a neurotransmitter-activated receptor, except that the "neurotransmitter" (retinal) is covalently linked to its binding site on the receptor molecule. In the dark, the "neurotransmitter" is in an inactive state (the folded isomer, 11-*cis* retinal), and so the receptor is not activated. Light converts the "neurotransmitter" to an active form (the unfolded isomer, all-*trans* retinal) and thus activates the receptor molecule. All subsequent signaling events are analogous to those of other G-protein–coupled receptor molecules.

The G-protein activated by photoisomerized rhodopsin, called **transducin**, is associated with the cytoplasmic surface of the rhodopsin-containing intracellular disks in the outer segments of the rod photoreceptors. Transducin is a **heterotrimeric G-protein,** consisting of three separate protein subunits. GTP binds to the **alpha subunit** to activate the G-protein, and the alpha subunit with GTP bound in turn mediates the G-protein's effects on intracellular second messenger levels. The **beta subunit** and the **gamma subunit** form an inhibitory duplex that binds to the inactive, GDP-bound form of the alpha subunit (in some cases, the beta-gamma complex also acts as a cellular signal in parallel with the alpha subunit when the triplex is dissociated). Thus, activation of the G-protein involves the replacement of GDP on the alpha subunit with GTP, and the dissociation of the beta-gamma subunit complex from the alpha subunit. This activating reaction is catalyzed by photoisomerized rhodopsin during phototransduction, as shown schematically in Figure 16.10. The activated transducin alpha subunit, with GTP bound, is then released by photoactivated rhodopsin, and the rhodopsin becomes free to interact with another molecule of inactive transducin and convert it to the active form.

As with other G-proteins in neurotransmitter-mediated signaling systems, the transducin alpha subunit targets an enzyme in the photoreceptor that is involved in controlling the levels of an intracellular second messenger. In this case, the target is **phosphodiesterase**, an enzyme that is also associated with the cytoplasmic face of the intracellular disks. Phosphodiesterase inactivates cyclic nucleotides (a common internal second messenger in cells) by breaking the cyclic phosphate bond and converting the molecule to a nucleoside monophosphate. The noncyclic form of the nucleotide molecule is not effective as an internal second messenger in cells. In photoreceptors, phosphodiesterase inactivates a cyclic nucleotide called **cyclic GMP.**

Figure 16.10
The linkage between photoactivated rhodopsin and the hydrolysis of cyclic GMP. The activated form of a molecule is indicated by an asterisk. Rh represents the rod photopigment, rhodopsin. The G-protein, transducin, is abbreviated T, and PDE indicates phosphodiesterase. See the text for a full description of all steps in the process.



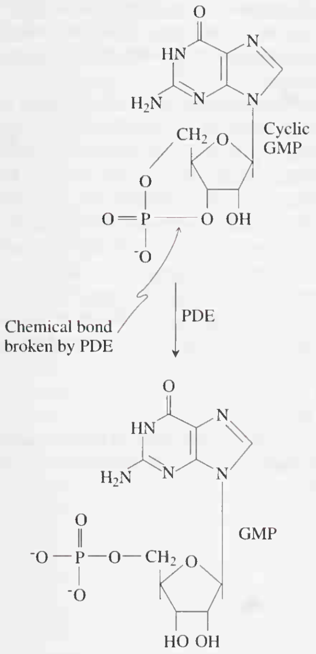
The hydrolytic reaction catalyzed by the phosphodiesterase is shown in Figure 16.11. The phosphodiesterase in the rod's outer segment is inactive in darkness, but becomes activated upon illumination by forming a complex with the GTP-bound form of the transducin alpha subunit (see Fig. 16.10). The activated phosphodiesterase then cleaves cyclic GMP at a rapid rate, reducing the cytoplasmic concentration of cyclic GMP in the photoreceptor outer segment. This reduction in cyclic GMP concentration causes the nonspecific cation channels in the plasma membrane of the outer segment to close.

The light-dependent ion channels are directly gated by cyclic GMP

Cyclic nucleotides, such as cyclic GMP and cyclic AMP, commonly affect cellular functions indirectly, by activating cyclic-nucleotide–dependent protein kinases, which in turn phosphorylate proteins to affect their functioning. In the case of phototransduction, however, cyclic GMP has a more direct effect on the ionic conductance of the outer segment. Cyclic GMP directly binds to specific sites on the cytoplasmic portion of the cation channel, causing the channel to open. Thus, the light-dependent ion channels are actually ligand-gated ion channels functionally similar to neurotransmitter-gated ion channels like the acetylcholine-activated channel of the neuromuscular junction. Unlike neurotransmitter-gated channels, in which ligand binding sites are located on the extracellular face of the ion channel, the binding site of the light-dependent channel faces the cell interior, where its controlling messenger is located.

The cyclic GMP–gated channel is thought to be formed by the combination of four identical protein subunits, each with a cyclic GMP–binding site on the cytoplasmic side of the subunit. For the channel to open, all four cyclic GMP–binding sites must be occupied. The cyclic GMP level is higher in the outer segment in darkness than it is in the light, when phosphodiesterase is activated. Thus, the probability that all four binding sites will be occupied by cyclic GMP will be higher in darkness, and more channels will be open. As a result, the photoreceptor cell is maintained at a more depolarized membrane potential in darkness. When the cyclic GMP level falls upon illumination, cyclic GMP is released from the binding sites, the channels close, and the photoreceptor hyperpolarizes.

Figure 16.11
The chemical structure of the internal messenger cyclic GMP (top), which is hydrolyzed to GMP (bottom) by the enzyme phosphodiesterase.



Turn-off mechanisms: restoring the dark state when illumination ceases

Because the photoreceptor cell must be able to signal that light has been turned off as well as on, mechanisms must exist to turn off the activated rhodopsin, transducin, and phosphodiesterase molecules. The transducin alpha subunit is not only a GTP-binding protein, but also a GTPase. Therefore, transducin has an inherent lifetime in the activated state, governed by the GTPase activity of the molecule. When transducin hydrolyzes the bound GTP into GDP plus inorganic phosphate, the transducin alpha subunit becomes inactive. In the GDP-bound form, the transducin alpha subunit cannot turn on the phosphodiesterase molecule to which it is bound, and the phosphodiesterase stops cleaving cyclic GMP (see Fig. 16.10). The inactive phosphodiesterase then dissociates from the transducin alpha subunit, which recombines with the beta and gamma subunits to reform the inactive form of the heterotrimeric G-protein shown at the top of the cycle in Figure 16.10. If photoactivated rhodopsin is still present, the transducin can be reactivated and enter the cycle for another round. In addition, the inactive phosphodiesterase can combine with a new activated alpha subunit of transducin and become active again, as long as rhodopsin continues to supply new GTP-bound alpha subunits (as in the continued presence of light, for example).

What happens to the molecule of rhodopsin that has absorbed a photon of light and been converted to the active form? Once 11-*cis* retinal has been isomerized to the all-*trans* form by light, it remains in this state. As a result, some mechanism is needed to inactivate the rhodopsin. Otherwise, each molecule of rhodopsin that has undergone photoisomerization would continue to activate transducin long after the light stimulus has disappeared. The key to rhodopsin turn-off lies in the uncoiled cytoplasmic tail of the molecule, where activated rhodopsin interacts with transducin. In addition to the transducin binding site, the conformation change in photoactivated rhodopsin reveals a number of **phosphorylation sites** on the amino acids found in this location. At these sites, phosphate groups can be covalently attached to the amino acids by an enzyme called a **kinase.** Such kinase-mediated protein phosphorylation reactions are a common mechanism by which the function of a protein molecule can be altered in cells.

In the case of rhodopsin, a specific kinase enzyme, called **rhodopsin kinase**, begins to attach phosphate groups to rhodopsin once the cytoplasmic tail becomes accessible as a result of the light-induced conformation change. The phosphorylated rhodopsin faces two possible fates. It can re-enter the transducin activation cycle and produce a new molecule of activated transducin, or it can encounter another protein called **arrestin**, which binds to the cytoplasmic tail of rhodopsin after phosphorylation. The greater the number of phosphate groups attached to rhodopsin, the higher the probability of arrestin binding. When arrestin attaches to rhodopsin, rhodopsin becomes unable to bind to transducin and thus is inactivated. This inactivation mechanism for photoisomerized rhodopsin is shown schematically in Figure 16.12,

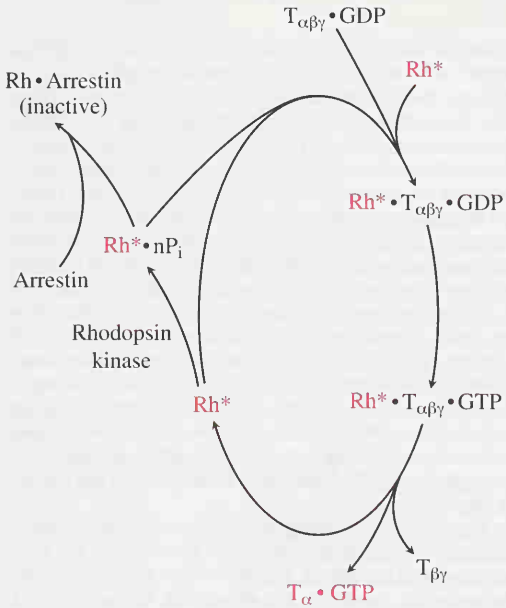

$T_{\alpha\beta\gamma}$ • GDP
Rh*
Rh • Arrestin (inactive)
Rh* • $T_{\alpha\beta\gamma}$ • GDP
Rh* • nP_i
Arrestin
Rhodopsin kinase
Rh*
Rh* • $T_{\alpha\beta\gamma}$ • GTP
$T_{\beta\gamma}$
T_α • GTP

Figure 16.12
The mechanism of inactivation of photoactivated rhodopsin. Abbreviations are the same as in Figure 16.10.

which reproduces the rhodopsin portion of the transduction cycle (see Fig. 16.10) but adds loops for phosphorylation and subsequent inactivation of rhodopsin.

Ultimately, the all-*trans* retinal of a photoisomerized rhodopsin molecule must be replaced with a new molecule of 11-*cis* retinal to regenerate the dark form of rhodopsin and to recycle the pigment molecule for future use in detecting light. After a period of time (minutes), the all-*trans* retinal dissociates from the opsin protein, freeing the retinal-binding site on opsin for chemical combination with another molecule of 11-*cis* retinal. The free all-*trans* retinal is converted back to the 11-*cis* form, in a reaction catalyzed by an isomerase enzyme. The conversion of all-*trans* to 11-*cis* retinal mostly takes place in specialized epithelial cells that surround the photoreceptor outer segments and provide the photoreceptors with a continuous supply of 11-*cis* retinal for the regeneration of used rhodopsin. Thus, the all-*trans* retinal is shuttled through the extracellular space to the epithelial cells, which take it up and enzymatically convert it to the 11-*cis* isomer. The 11-*cis* retinal is then shuttled back through the extracellular space to the photoreceptor outer segment. Specialized extracellular retinal-binding proteins act as molecular chaperones during this shuttling of retinal between the photoreceptors and the epithelial cells.

To restore the dark state of the photoreceptor after illumination has been turned off, the cyclic GMP level must be restored from the low level reached in the light to the higher level present during darkness; this restoration allows the cyclic GMP–gated channels to reopen and depolarize the cell. Cyclic nucleotides are produced by enzymes called **nucleotide cyclases,** which convert nucleoside triphosphate molecules to the corresponding cyclic nucleoside monophosphate. The enzyme that manufactures cyclic GMP in the photoreceptor outer segment using GTP as the raw material is called **guanylate cyclase.** The concentration of cyclic GMP in the outer segment—and thus the fraction of cyclic GMP–gated ion channels that are open—depends on the balance between production of cyclic GMP by guanylate cyclase and degradation of cyclic GMP by phosphodiesterase. In the light, phosphodiesterase is activated, the degradation rate of cyclic GMP is high, and the level of cyclic GMP is low in the outer segment. When illumination ceases, however, the activity of the phosphodiesterase falls and the level of cyclic GMP rises as the cyclase restores the resting concentration in darkness.

The rate at which guanylate cyclase produces cyclic GMP is also regulated by light, albeit in an indirect way. In the presence of light, the cyclase activity is higher than in darkness. This change in enzyme activity with lighting conditions is mediated via changes in intracellular calcium concentration that accompany the transition from dark to light. As noted earlier, nonspecific cation channels keep the photoreceptor depolarized in darkness. Under normal conditions, most of the current flowing through open channels is carried by an influx of sodium ions. In addition, calcium ions carry a significant portion of the inward ionic current through the channels. Thus, the calcium concentration inside the outer segment is higher in the dark, when the nonspecific cation channels are open, than it is in the light, when the channels are closed.

The rate of cyclic GMP production is increased by a modulatory protein, which binds to the enzyme and increases its catalytic rate. The modulatory protein is a calcium-binding protein, which can interact with and stimulate guanylate cyclase only in its calcium-free form. The calcium-free form prevails in the presence of illumination, when the calcium concentration inside the outer segment is low. In the dark, when internal calcium levels are higher, calcium binds to the modulatory protein, preventing the interaction between the modulatory protein and cyclase and ensuring that cyclase activity is not enhanced. In this way, the calcium level in the outer segment provides feedback regulation of the cyclic GMP production rate, based on the number of open cyclic GMP-gated channels (that is, the source of calcium ions).

LIGHT RESPONSES OF SECOND-ORDER RETINAL NEURONS

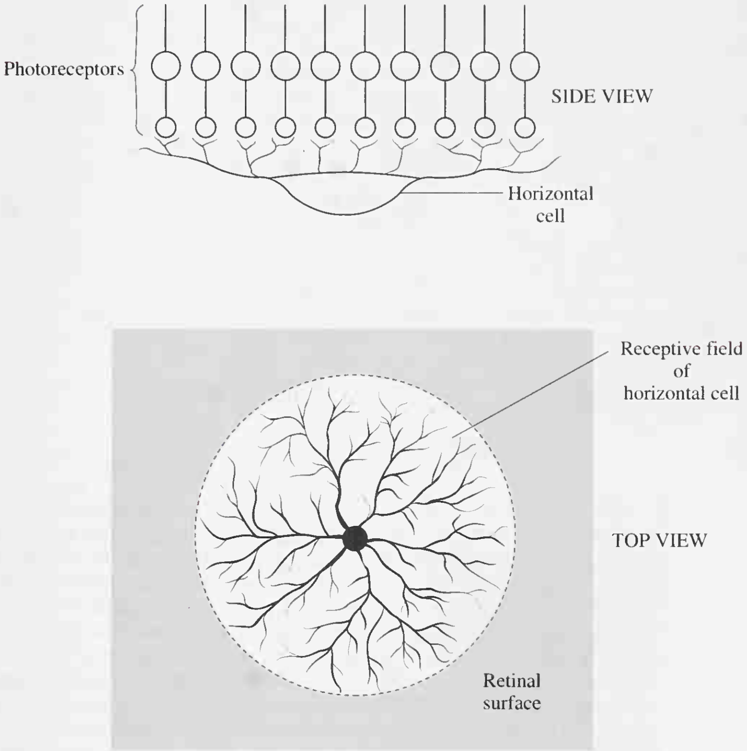
Horizontal cells

The photoreceptors make synaptic connections with two different types of interneurons: bipolar cells and horizontal cells (see Fig. 16.2). The synaptic terminals of the photoreceptors release the neurotransmitter glutamate. Because the photoreceptors are depolarized in darkness and hyperpolarized in light, the rate of glutamate release is high in darkness and reduced by illumination. Therefore, the light response of the neurons that receive inputs from the photoreceptors represents a reaction to *removal* of glutamate. In the horizontal cells, glutamate opens nonspecific cation channels. Thus, like the photoreceptors, the horizontal cells are depolarized in darkness—when glutamate is being released by the photoreceptors—and hyperpolarize upon illumination.

The horizontal cells have widely spreading dendrites that receive inputs from the photoreceptors in a correspondingly large area of the retina (Fig. 16.13). Light falling within this area of the retina, known the receptive field of the horizontal cell, produces hyperpolarization of the horizontal cell. As we discussed in chapter 14, all neurons that respond to sensory stimuli have a receptive field corresponding to the region of the sensory surface where stimuli affect the activity of the neuron. In the case of the visual system, the sensory surface consists of the photoreceptor cells of the retina. If a cell receives synaptic inputs from a group of photoreceptors, its receptive field will be defined as the region of retinal surface encompassed by that group of photoreceptor cells.

In the case of horizontal cells (see Fig. 16.13), the situation is somewhat more complicated. These cells are electrically coupled via gap junctions to neighboring horizontal cells, forming an electrically coupled lateral network. When light falls on the photoreceptors that make synaptic contacts directly onto a particular horizontal cell, some of the resulting hyperpolarization in that horizontal cell will spread laterally via the electrical junctions into neighboring horizontal cells, which do not receive direct synaptic

Figure 16.13
The receptive field of a horizontal cell.

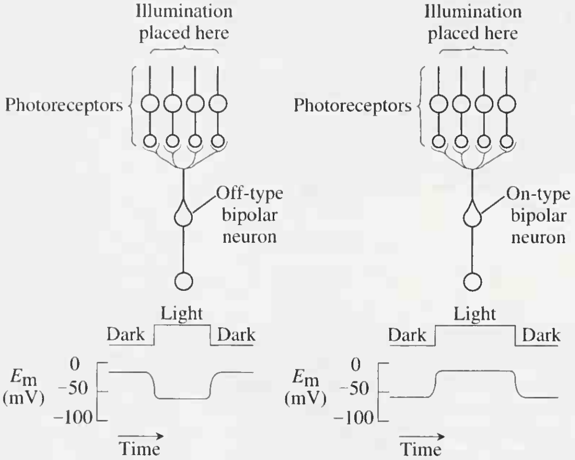


inputs from that set of photoreceptors. Thus, the neighboring horizontal cells will hyperpolarize as well, even though their own directly connected photoreceptors received no light. For this reason, the receptive field of a horizontal cell is actually larger than would be expected if its membrane potential were affected only by light falling on the directly connected group of photoreceptors.

Two classes of bipolar neurons: off-type and on-type

The other type of second-order neuron in the retina is the bipolar cell. Like the horizontal cells, bipolar cells receive direct synaptic inputs from photoreceptors (Fig. 16.14). Thus, light falling on each group of photoreceptors will

Figure 16.14
Light responses of off-type and on-type bipolar neurons.

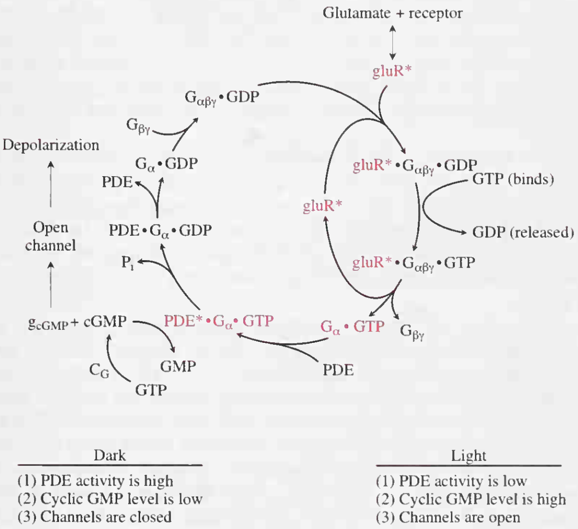


influence the membrane potential of the bipolar neuron. Two classes of bipolar neurons are distinguished on the basis of the change in membrane potential elicited by illumination of the directly connected photoreceptors. **Off-type** or **hyperpolarizing bipolar cells** respond in the same way as the horizontal cells to illumination: in the dark, these bipolar neurons have a relatively positive membrane potential (for example, −20 to −30 mV), which becomes more negative in the presence of light (see Fig. 16.14). Glutamate released by the photoreceptors directly binds to and opens glutamate-gated nonspecific cation channels in the dendrites of off-type bipolar neurons. The cells remain relatively depolarized in darkness, which is when the synaptic terminals of the photoreceptors are releasing glutamate at a higher rate. In contrast, **on-type** or **depolarizing bipolar cells** have the opposite response to light. In darkness, these bipolar cells have a relatively negative membrane potential (about −60 to −50 mV); upon illumination, they depolarize (see Fig. 16.14).

The depolarizing light response of the on-type bipolar cells provides an interesting twist on the more usual mechanisms of synaptic transmission. In this case, glutamate *suppresses* the activation of nonspecific cation channels. When light decreases the release of glutamate from the photoreceptor synaptic terminals, the suppression of the cation channels is removed and the cation channels open, depolarizing the bipolar cell. The linkage between the glutamate receptor in the dendrites of the on-type bipolar neuron and the nonspecific cation channel is indirect. The glutamate receptor is a member of the G-protein–coupled family of receptors; when glutamate binds to the receptor, it activates a G-protein. The activated G-protein targets phosphodiesterase, just like the phototransduction system in the photoreceptor discussed earlier in this chapter. Figure 16.15 summarizes the overall effect of glutamate in the on-type bipolar neurons. The phosphodiesterase of the bipolar neuron hydrolyzes and inactivates the internal messenger cyclic GMP (just as in the photoreceptors). The analogy with phototransduction extends even further, as cyclic GMP directly binds to and opens a type of cyclic GMP–gated ion channel similar to the one found in photoreceptor outer segments. Thus, the number of open cyclic GMP–gated channels—and hence the amount of depolarization—depends on the balance between degradation of cyclic GMP by activated phosphodiesterase and production of cyclic GMP by guanylate cyclase.

In the dark, photoreceptor synaptic terminals release glutamate at a high rate, glutamate is available to bind to and activate the glutamate receptors, and so the phosphodiesterase is strongly activated (see Fig. 16.15). Because the level of cyclic GMP in the bipolar neuron remains low, most of the cyclic GMP–gated channels stay closed and the cell membrane potential is relatively negative. In the light, the photoreceptors stop releasing glutamate, the glutamate concentration in the synaptic cleft falls, and the supply of activated glutamate receptors to initiate the cycle shown in Figure 16.15 is cut

Figure 16.15
The postsynaptic response to glutamate in on-type bipolar neurons.



off. Consequently, the activity of the phosphodiesterase is reduced and the balance between degradation and synthesis of cyclic GMP shifts to favor synthesis. As cyclic GMP levels rise, more cyclic GMP–gated channels open, and the bipolar neuron depolarizes.

Receptive field of bipolar neurons

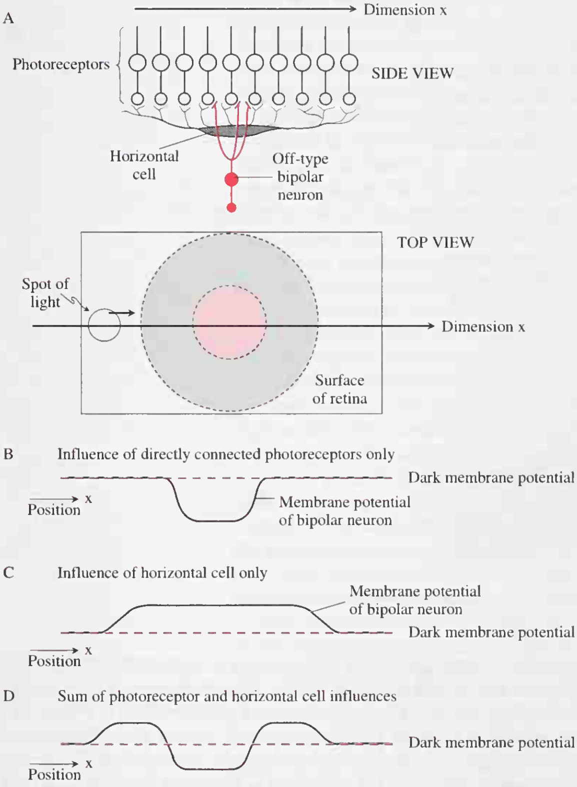
As we have just discussed, light falling on the photoreceptors that make synaptic connections with bipolar cell dendrites depolarizes the on-type bipolar cells and hyperpolarizes the off-type bipolar cells. The indirect effects of illumination falling outside this region of directly connected photoreceptors must also be considered, however. These indirect effects are mediated via the connections made by the lateral interneurons, the horizontal cells. Recall that horizontal cells have widely spreading dendrites that cover a large area of the retina. Bipolar cells usually include much more restricted dendrites that receive direct connections from the photoreceptors in a much smaller region of retina, as illustrated in Figure 16.16. If we superimpose the regions of photoreceptors contacting a horizontal cell and a bipolar cell (both located at the same position in the retina), we would see the larger spatial extent of the horizontal cell receptive field (see Fig. 16.16).

Like the photoreceptors, the horizontal cells depolarize in darkness and hyperpolarize in response to illumination. Also like the photoreceptors, neurotransmitter release from the horizontal cells is highest in darkness and is reduced by illumination. The synaptic connectivity of the horizontal cells and the postsynaptic action of the horizontal cell neurotransmitter are arranged so that hyperpolarization of the horizontal cell (that is, the effect produced by light in the horizontal cell) generates a response in the bipolar cells that is the *opposite* of the effect produced in the bipolar cell by illumination centered at the location of the bipolar cell. In other words, the horizontal cells always produce negative feedback onto the bipolar neurons. An off-type bipolar cell is depolarized when the horizontal cells hyperpolarize, while the on-type bipolar cells are hyperpolarized when the horizontal cells depolarize.

Figure 16.17 illustrates a simple mechanism for negative feedback from horizontal cells to bipolar cells. The synaptic terminals of photoreceptors receive inputs from the horizontal cells, which are themselves the synaptic targets of the photoreceptors. This type of feedback synapse, in which a neuron makes a synaptic contact onto its own inputs, is commonly encountered in neuronal information processing in the retina and in the nervous system in general.

Let's examine how the horizontal cell feedback synapse is thought to produce the negative feedback effect on the bipolar neurons, even in the absence of a direct connection between the horizontal cells and the bipolar neurons. In many species, at least some horizontal cells release GABA as their neurotransmitter at the synaptic connection onto the synaptic terminal of the photoreceptors. GABA directly binds to and opens GABA-gated chloride channels in the membrane of the photoreceptor terminal. When darkness causes the horizontal cells to depolarize, more GABA is released at the feedback synapse, increasing the chloride permeability of the photoreceptor.

Figure 16.16
The receptive field of an off-type bipolar neuron. When a spot of light is moved across the receptive field in the direction of the arrow shown in A, it stimulates photoreceptors in the surround region of the receptive field (gray) and then stimulates the group of photoreceptors that make direct synaptic connections with the bipolar cell (pink). When light falls on the central region of the receptive field, the bipolar neuron hyperpolarizes (B). Light falling within the receptive field of the horizontal cell produces the opposite effect (C). The response of the photoreceptor as a function of the light position is the sum of these two influences (D).



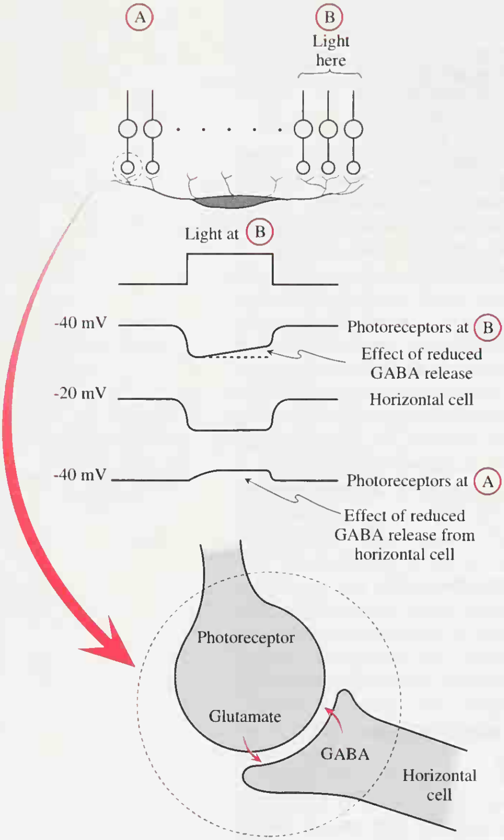


Figure 16.17
The contribution of horizontal cell synaptic input to the light response of photoreceptors.

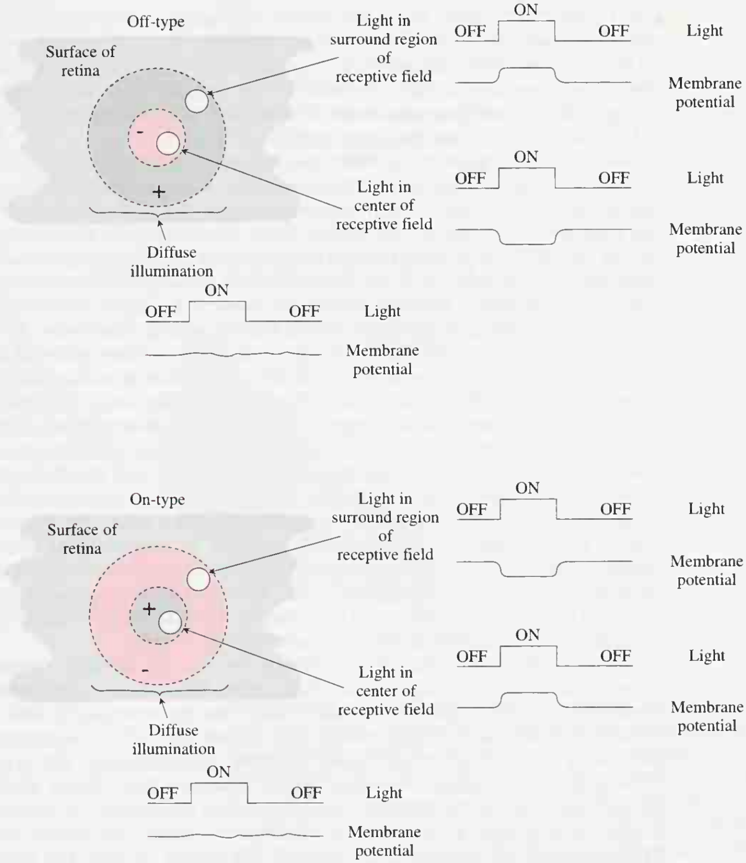
This process adds a hyperpolarizing influence to the photoreceptor in darkness, making the membrane potential of the photoreceptor—although depolarized, as described earlier in this chapter—less positive than it would be in the absence of GABA released by the horizontal cells. Upon illumination, both the photoreceptors and the horizontal cells to which they are connected hyperpolarize, reducing the release of GABA from the horizontal cells and *removing* a hyperpolarizing influence on the photoreceptor. Thus, during sustained illumination, the membrane potential of the photoreceptor first hyperpolarizes (by an amount dependent on light intensity) and then moves to a somewhat more depolarized level, as GABA release from the horizontal cells is reduced (again by an amount dependent on the degree of hyperpolarization in the horizontal cells) (see Fig. 16.17).

In addition, consider what happens if light is placed to the side of a particular photoreceptor (rather than directly onto it), but still within the receptive fields of the nearby horizontal cells. Because the light does not fall directly onto the photoreceptor in question, no hyperpolarization of the photoreceptor is produced by direct illumination (the position marked A in Figure 16.17). Nevertheless, the horizontal cell will still be hyperpolarized because of the light falling on the other photoreceptors (the position marked B in Figure 16.17). Thus, less GABA will be released by the horizontal cell onto the synaptic terminals of the photoreceptors at position A, even though no illumination strikes that position. The photoreceptors at that position will *depolarize* in response to light displaced to the side. In other words, light falling on the surrounding portion of the retina will have the opposite effect as light falling directly on the photoreceptors.

Return now to Figure 16.16, which shows how the synaptic arrangement illustrated in Figure 16.17 affects bipolar neurons. Consider first an off-type bipolar cell. If a small spot of light is placed so that it falls on the photoreceptors from which the bipolar cell receives direct synaptic inputs, the off-type bipolar cell will hyperpolarize because less glutamate will be released onto its dendrites by the directly connected photoreceptors. If the light is moved to the side, so that it no longer falls onto the directly connected group of photoreceptors, its hyperpolarizing influence on the bipolar neuron disappears. This effect of the directly connected photoreceptors on the membrane potential of the bipolar neurons is shown in Figure 16.16B as a function of position of the illuminating spot on the retinal surface. When the light falls outside the region of the directly connected photoreceptors, but still within the receptive field of the horizontal cell (the gray region in Figure 16.16A), then the photoreceptors that are directly connected to the off-type bipolar neuron will depolarize in response to illumination (see Fig. 16.17). This depolarization will increase the release of glutamate from their synaptic terminals. As a result, the bipolar neuron will depolarize in response to illumination. This depolarizing effect created by the indirect action of the horizontal cell is shown as a function of the position of illumination in Figure 16.16C. The effect of illumination at any particular position on the retina will then consist of the sum of the competing photoreceptor and horizontal cell influences (see Fig. 16.16D).

The receptive field of the off-type bipolar neuron will therefore consist of two regions: a central region where light causes the cell to hyperpolarize (because of decreased glutamate release from the photoreceptors) and a concentric surrounding region where light causes the cell to depolarize (because of increased glutamate release from the photoreceptors). This type of receptive field is called a **center-surround receptive field.** Figure 16.18 shows a top view of the receptive field that would be mapped by placing a small spot of light at different positions on the retina and noting the light's effect on the membrane potential of the bipolar neuron. The most effective stimulus for producing hyperpolarization of the bipolar neuron will not be a diffuse illumination across the entire receptive field, but rather a central bright region surrounded by a region of darkness. In other words,

Figure 16.18
Receptive fields and light responses of off-type and on-type bipolar neurons. Light placed in the central portion of the receptive field hyperpolarizes the off-type bipolar cell and depolarizes the on-type bipolar neuron. Conversely, light placed in the surround portion of the receptive field depolarizes the off-type bipolar cell and hyperpolarizes the on-type bipolar cell. In both cases, the area where light hyperpolarizes the cell is shown in pink, and the region where light depolarizes the cell is shown in gray. Diffuse illumination that covers the entire receptive field has little effect on the membrane potential of either type of bipolar neuron.



the information being transmitted from a bipolar neuron of this type really concerns brightness contrast on the retinal surface. For an on-type bipolar neuron, the receptive field would still have the same center-surround organization, but the signs of the responses in the center and surround regions would be reversed (see Fig. 16.18).

For both on-type and off-type bipolar cells, the postsynaptic effect of light placed in the central region is that produced by decreasing the release of glutamate from the photoreceptor synaptic terminals, while the effect of light placed in the surround region is that produced by increasing glutamate release. Because the lateral inhibitory effect mediated by the horizontal cells targets the synaptic terminal of the photoreceptor and influences the bipolar neuron by affecting presynaptic glutamate release, illumination in the surround region of the receptive field is always antagonistic to illumination in the center, regardless of whether glutamate depolarizes or hyperpolarizes the bipolar cell.

This mechanism is thought to account for the center-surround organization of the bipolar cell receptive field in the retinas of some animal species, but it is not universally true in all species. In some cases, the postsynaptic target of the horizontal cells is the bipolar neurons themselves, rather than the photoreceptor synaptic terminal. In addition, not all horizontal cells release GABA as their neurotransmitter. In those cases, the exact mechanism responsible for the antagonism between the center and the surround of the receptive field remains uncertain.

LIGHT RESPONSES OF AMACRINE CELLS

Just as lateral interconnections mediated by the horizontal cells appear at the level of the photoreceptor output synapses, lateral interconnections are also noted at the level of the output synapses of the bipolar cells. In this case, the neurons mediating the lateral interconnections are amacrine cells (see Fig. 16.2). These cells receive inputs from the bipolar cells and make feedback synapses onto the terminals of the bipolar neurons, again analogous to the reciprocal connections between photoreceptors and horizontal cells. Like horizontal cells, at least some amacrine cells use GABA as their neurotransmitter. Such amacrine cells make reciprocal synapses onto bipolar cell synaptic terminals, which have GABA-gated chloride channels like those found in the terminals of photoreceptors (as discussed earlier). Thus, the amacrine cells are lateral inhibitory interneurons, which produce effects at the level of the bipolar cell output synapses that are analogous to those produced by the horizontal cells at the level of the photoreceptor output synapses.

Amacrine cells depolarize in response to changes in light intensity within their receptive fields. The dendrites of these cells commonly extend for a considerable distance in the retina, receiving synaptic inputs from bipolar cells in a broad area. Consequently, the receptive fields of the amacrine cells are typically quite large, corresponding to the region covered by all photoreceptors connected to the entire set of bipolar neurons sampled by the amacrine cell. Glutamate released from the synaptic terminals of the bipolar neurons opens glutamate-gated nonspecific cation channels and depolarizes the amacrine cell. Some amacrine cells, called on-type amacrine cells, receive inputs from only on-type bipolar cells. Such amacrine cells depolarize at the onset of illumination, when the on-type bipolar cells depolarize and release transmitter. In contrast, off-type amacrine cells receive synaptic inputs from only off-type bipolar cells and therefore depolarize when illumination ends. Another type, called on-off amacrine cells, receives synaptic inputs from both on-type and off-type bipolar cells. These different light responses of amacrine cells are shown in Figure 16.19.

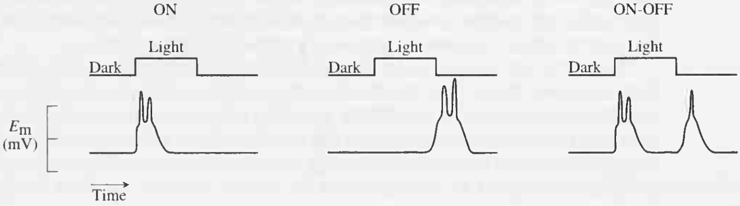
Figure 16.19 also illustrates another characteristic of the light responses of amacrine cells. Note that the depolarizing light responses are strongly transient, producing a depolarization only briefly following a change in illumination level. Most amacrine cells exhibit transient light responses of this type. If the depolarization produced by the onset or termination of illumination is sufficiently large, amacrine cells produce action potentials in response to the synaptic depolarization (see Fig. 16.19). The action potentials in amacrine cells result from voltage-dependent sodium channels, as described in chapters 5 and 6. This instance is the first time we have mentioned action potentials in conjunction with the light responses of the retinal neurons. In the photoreceptors, horizontal cells, and bipolar cells, the changes in membrane potential produced by illumination spread electrically throughout the cell without requiring action potentials.

LIGHT RESPONSES OF RETINAL GANGLION CELLS

The output from the eye is transmitted to the brain via the axons of the retinal ganglion cells, which come together to form the optic nerve (cranial nerve II). Because the information carried by the ganglion cells must be

Figure 16.19

Light responses of three types of amacrine cells. The on-type produces a transient depolarization at light onset, the off-type produces a depolarization when the light is turned off, and the on-off-type produces transient depolarizations at both the onset and termination of illumination. Amacrine cells also fire action potentials when the depolarizing synaptic response is sufficiently large.



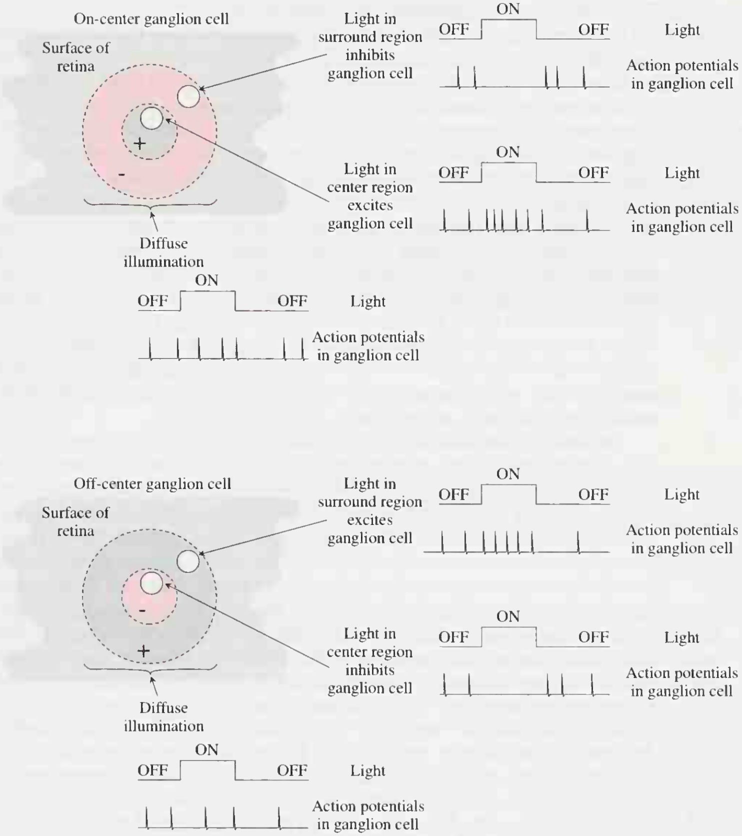
carried over long distances, the electrical signal used by ganglion cells is the action potential—the long-distance signal in the nervous system. Therefore, information about light falling on the retina must be coded in the frequency of action potentials fired by the retinal ganglion cells. As we shift our attention to the output cells of the retina, the light responses we will encounter will be represented as changes in action potential activity, rather than the depolarizing and hyperpolarizing synaptic potentials noted with bipolar neurons and horizontal cells. Keep in mind, however, that the changes in action potential firing in the ganglion cells reflect the combined excitatory and inhibitory synaptic interactions from the bipolar cells and amacrine cells that make synaptic connections with the ganglion cells.

Light responses of ganglion cells are classified into the same general categories as those of amacrine cells, based on whether a cell is excited by an increase in light intensity, a decrease in light intensity, or both. In addition, light responses in ganglion cells can be either sustained for the duration of the stimulus or transient in nature. These response characteristics are summarized in Figure 16.20. Ganglion cells can have complex response properties as well. For instance, some cells respond only to a light moving in a particular direction across the retina. These motion-sensitive ganglion cells are analogous to the motion-sensitive cortical neurons in the somatosensory system discussed in chapter 15. Motion selectivity in the visual system probably arises via synaptic arrangements like those that produce the motion-selective cells in the touch sensory pathway—that is, via lateral inhibitory connections made selectively to one side (see Fig. 15.15 on page 357). Other ganglion cells respond to light by firing action potentials at a rate proportional to the overall average level of illumination falling on a wide area of retina, which suggests that these cells inform the brain about the average light intensity, or luminance, of the visual world.

The sizes of receptive fields of ganglion cells vary widely. Some ganglion cells receive inputs from only a single bipolar neuron, while others receive inputs from thousands of bipolar cells. The receptive fields of ganglion cells commonly have the concentric center-surround organization described previously for bipolar neurons. This organization is illustrated in Figure 16.20.

Light in the center of the receptive field of an **on-type ganglion cell** excites the cell, increasing the frequency of action potential firing, while light in the surrounding region inhibits the cell. Conversely, light in the center of the receptive field of an **off-type ganglion cell** inhibits the cell, while light in the surrounding region excites the cell. For both types of ganglion cells, a diffuse light across the entire receptive field has little effect. For an on-type ganglion cell, the stimulus that best excites the cell would be a spot of light that fills the central part of the receptive field, surrounded by darkness. For an off-type ganglion cell, the greatest excitation would result from a dark spot on a bright background. In both cases, the ganglion cell signals the brain about the spatial contrast in light intensity at the position of the ganglion cell's receptive field. In the visual world, contrast in light intensity typically defines the edge of an object, and so information about intensity contrast is important to the visual system in defining object shape and location in the visual world.

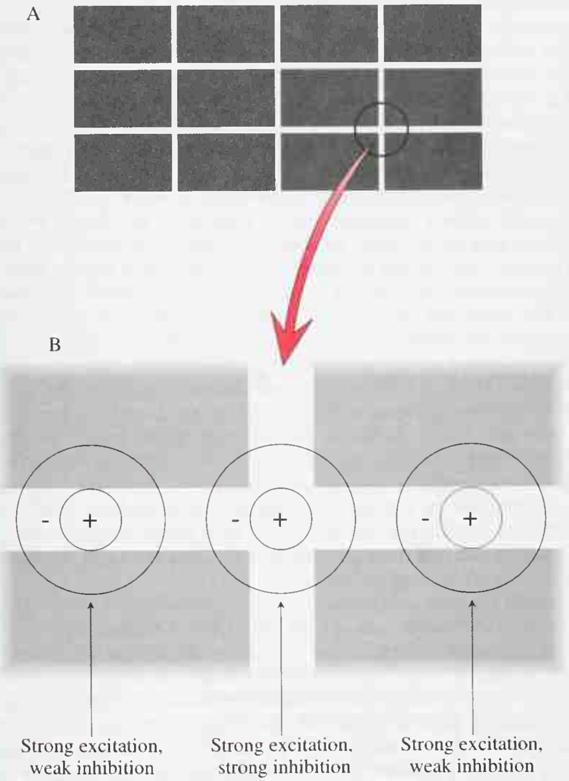
Figure 16.20
Receptive fields of on-center and off-center ganglion cells. Light placed in the center of the receptive field increases the rate of action potential firing in on-center cells and decreases the rate of action potential firing in off-center cells. Light in the surround region of the receptive field has the opposite effect, exciting off-center cells and inhibiting on-center cells. In both cases, the ganglion cells fire action potentials at a slow rate even without illumination. This "spontaneous" firing allows the nervous system to distinguish both increases and decreases in firing rate. In addition, diffuse illumination applied to the entire receptive field produces only a weak light response in the ganglion cells.


On-center ganglion cell
Surface of retina
+
-
Light in surround region inhibits ganglion cell
ON
OFF
OFF
Light
Action potentials in ganglion cell
Light in center region excites ganglion cell
ON
OFF
OFF
Light
Action potentials in ganglion cell
Diffuse illumination
ON
OFF
OFF
Light
Action potentials in ganglion cell
Off-center ganglion cell
Surface of retina
-
+
Light in surround region excites ganglion cell
ON
OFF
OFF
Light
Action potentials in ganglion cell
Light in center region inhibits ganglion cell
ON
OFF
OFF
Light
Action potentials in ganglion cell
Diffuse illumination
ON
OFF
OFF
Light
Action potentials in ganglion cell

In extracting information about the spatial pattern of light intensity, the visual system sometimes perceives differences in light intensity when no such difference is actually present in the stimulus. The center-surround organization of the ganglion cell receptive fields produces some of these illusions, including the one illustrated in Figure 16.21. In the figure, black

Figure 16.21

A visual illusion that arises from the center-surround organization of the ganglion cells in the human retina. Looking at the array of black rectangles (A), you observe a gray spot at each intersection of the grid of white lines defined by the spaces between adjacent rectangles. This perception of reduced light intensity is produced when your brain interprets the outputs of retinal ganglion cells whose receptive fields are arranged as shown in B.


A
B
-
+
-
+
-
+
Strong excitation, weak inhibition
Strong excitation, strong inhibition
Strong excitation, weak inhibition

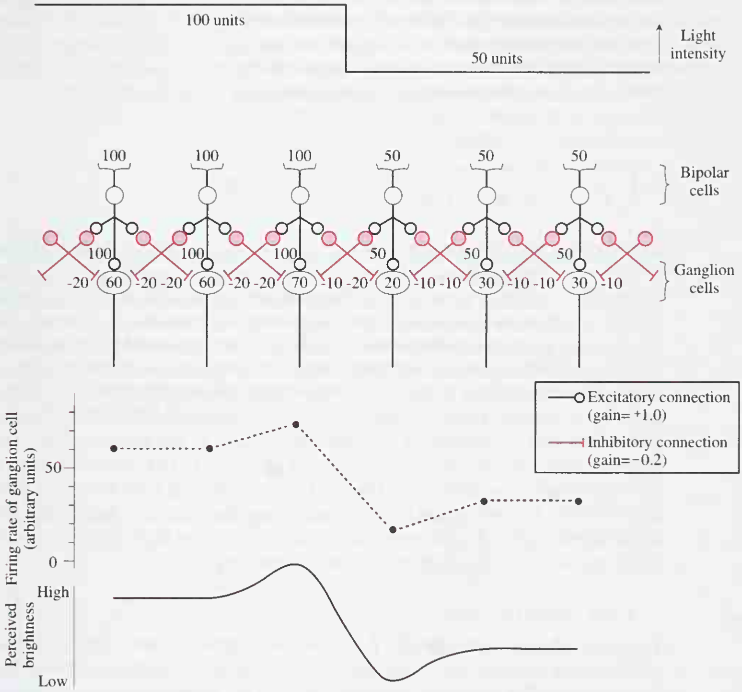
rectangles are separated by uniform white lines. As you look at the array of rectangles, you will notice a dim gray spot at each intersection of the white lines. These gray spots are not present in the stimulus but are "created" in the retina by the center-surround receptive fields of the retinal ganglion cells. The basis of this effect is illustrated schematically in the lower part of Figure 16.21, which shows receptive fields for three on-center ganglion cells. The two cells on each side, away from the corners of the rectangles, have their centers fully illuminated, but their surrounds lie mostly in darkness. As a result, these ganglion cells are strongly excited but only weakly inhibited, giving rise to a relatively high firing rate. A different situation prevails in the case of the ganglion cell that has its receptive field at the intersection of the two white lines, however. For this cell, the center is fully illuminated, but the surround is also strongly illuminated. The cell fires action potentials at a lower rate than the two other ganglion cells to each side. The visual nervous system interprets the lower firing rate of the central cell as a lower light intensity, causing us to perceive a gray area at the intersection.

In chapters 14 and 15, we learned how lateral inhibitory connections enhance the contrast between regions where the sensory stimulus changes intensity. As noted in this chapter, lateral inhibitory synapses are found at two levels in the retina: the horizontal cells at the outputs from the photoreceptors, and the amacrine cells at the outputs from the bipolar cells. To see how this arrangement aids in the detection of borders between regions of differing light intensity on the surface of the retina (that is, an edge), examine the set of hypothetical neural connections in Figure 16.22. An array of ganglion cells receives excitatory inputs from a set of on-type bipolar neurons, which also excite lateral inhibitory neurons that inhibit the ganglion cells on each side. On the left portion of the array, each bipolar neuron in that region receives 100 units of excitation; on the dimmer right-hand portion of the array, the bipolar cells receive 50 units of excitation (the "excitation units" are arbitrary and are used only to illustrate the neuronal calculations performed at the synaptic interconnections). Each excitatory synapse transmits 100% of the incoming excitation to the postsynaptic cell, while each inhibitory synapses *subtracts* 20% of the incoming excitation from the total amount of excitation in the postsynaptic cell. Thus, each ganglion cell within the brighter region receives 100 units of excitation from the bipolar neuron, while having 20 units subtracted by each of the two inhibitory inputs (20% of 100 subtracted from each side), for a total of 60 units of excitation. Within the dimmer region, each ganglion cell receives 50 units of excitation, while inhibition subtracts 20 units (10 units from each side), for a total of 30 units of excitation.

Now consider the two ganglion cells in the array whose receptive fields are located just at the border between the brighter and dimmer regions. For the ganglion cell on the bright side of the border, the bipolar cell provides 100 units of excitation, while the inhibitory interneuron from the left subtracts 20 units (20% of 100). The inhibitory interneuron from the right receives its excitatory drive from the dim side of the border, and so subtracts only 10 units (20% of 50). Consequently, the ganglion cell on the bright side of the border receives a total of 70 units of excitation. For the ganglion cell

Figure 16.22

Lateral inhibitory connections enhance the perceived brightness contrast at a border between a lighter and a darker region. The spatial arrangement of light intensity falling on the retina is shown on the top, with an array of bipolar cells and ganglion cells shown below. In this schematic example, the excitatory connections from the bipolar neurons are assumed to transmit 100% of the "excitation units" produced in the bipolar neuron by the illumination to the postsynaptic cell. The inhibitory connections from the inhibitory interneurons (red) are assumed to subtract 20% of the "excitation units" in the inhibitory interneuron from the postsynaptic ganglion cell. The resulting rates of action potential firing in the ganglion cells are given by the dashed line. The visual system then interprets the firing rates of the ganglion cell to generate the perceived pattern of brightness illustrated in the bottom graph.



on the dim side of the border, the bipolar cell provides 50 units of excitation, while the two inhibitory connections subtract a total of 30 units (20 from the left and 10 from the right). Thus, the two ganglion cells at the border differ from their neighbors within the uniformly illuminated regions on each side, with the ganglion cell on the bright side of the edge being more strongly excited and the ganglion cell on the dim side being less strongly excited (see Fig. 16.22).

When the rest of the visual system reviews the output of the array of ganglion cells, it interprets the level of activity in each ganglion cell as reflecting the light intensity within the receptive field at that point. Thus, the perceived brightness of the stimulus parallels the pattern of neural activity shown in Figure 16.22. Because the ganglion cell just on the brighter side of the edge has more activity compared with its neighbors to the left and the ganglion cell on the dimmer side has less activity than its neighbors to the right, a human observer looking at a step change in light intensity like that in Figure 16.22 perceives a brighter band on the bright side of the edge and a darker band on the dim side. In other words, the lateral inhibitory synaptic connections within the retina increase the perceived contrast between the bright and dim sides. This enhanced detectability of regions where light intensity changes establishes the functional value of the lateral inhibitory connections that are so commonly found in neuronal synaptic processing in the visual system.

COLOR VISION

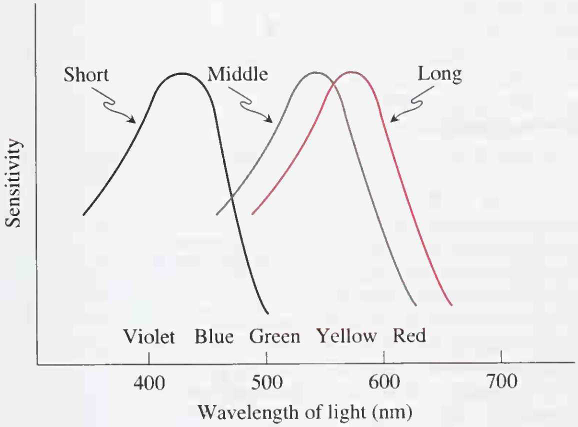
To this point, we have focused on the detection of light, determination of relative light intensity, and processing of information about spatial patterns of illumination that reach the retina. These clearly important aspects of visual system function are required to obtain information about the visual world. Indeed, many quite successful animal species have survived and prospered with visual systems that process *only* information about spatial patterns of illumination, without reference to the *color* of the illumination. (Can your cat catch a butterfly?) Humans know, however, that information about the *color* of an object is also vital in discerning and identifying parts of the environment. The physical characteristic of the stimulus that gives rise to the perceived color is the wavelength composition of the light that is reflected from or transmitted by the object. To understand how the neurons of the retina can distinguish different wavelengths of light, we need to return to the class of photoreceptors introduced earlier in the chapter: the cone photoreceptors.

Cone photoreceptors

The cone photoreceptors differ from the rod photoreceptors not only morphologically (see Fig. 16.3), but also in the types of photopigment molecules they contain. The rod photoreceptors contain the photopigment rhodopsin. Humans possess three types of cones, each of which contains a unique type of photopigment in its outer segments. In all three types of cone photopigment, the light-absorbing chromophore molecule is the same as in rhodopsin: 11-*cis* retinal. The opsin protein portion of the molecule differs slightly for the three types of cone photoreceptors, however.

Because the interaction between the opsin protein and the chromophore group determines the wavelength of light that is absorbed best by the chromophore, the different opsin proteins produce different **spectral sensitivities** for each of the three cone photopigments. The sensitivity of the three pigments of human cones to light of different wavelengths is illustrated in Figure 16.23. One type of photopigment absorbs light best at about 420 nm, one type has highest sensitivity at approximately 530 nm, and the third is most sensitive to light at a wavelength near 560 nm. The cones that contain the 420-nm pigment are called **S-cones** (for short-wavelength cones; "short" refers to their sensitivity to short wavelengths, not their size). The cones containing the 530-nm pigment are called **M-cones** (for middle-wavelength cones). The cones that have the 560-nm pigment are called **L-cones** (for, you guessed it, long-wavelength cones). These cones are also called **blue cones**, **green cones**, and **red cones**, respectively, because the S-cone pigment is most sensitive in the blue portion of the visible spectrum (at short wavelengths), the M-cone pigment is most sensitive in the green portion of the spectrum, and the L-cone photopigment is the most sensitive in the red portion of the spectrum (at longer wavelengths). Most visual neuroscientists prefer the "short," "middle," and "long" terminology, however. By comparison, the photopigment of the rods (rhodopsin) is most sensitive to light at a wavelength of 500 nm.

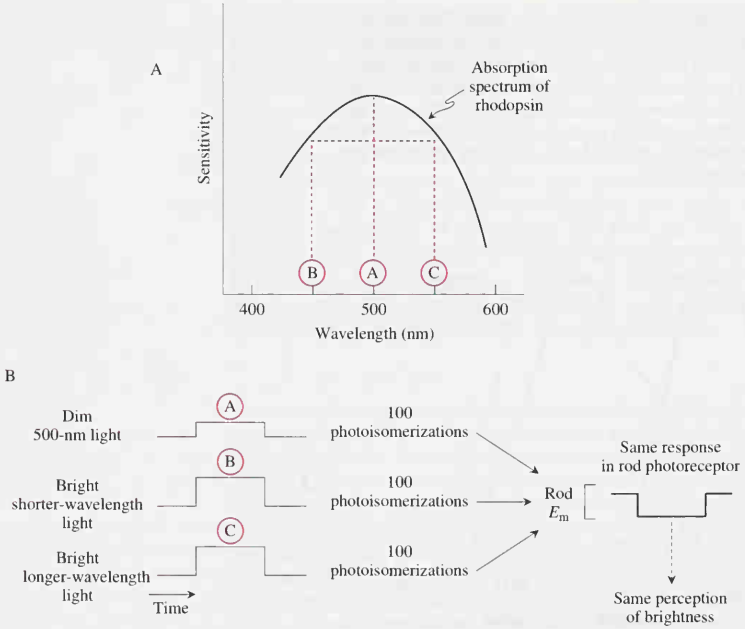
Figure 16.23
The sensitivity of the three cone photopigments to lights of different wavelengths in the visual spectrum. The cones sensitive to short-wavelength light have a photopigment that absorbs light best in the violet and blue portion of the visual spectrum (black curve). The cones sensitive to long-wavelength light have a pigment that absorbs best in the yellow and red part of the spectrum (red curve). The cones sensitive to middle-wavelength light have a photopigment that absorbs best in the green and yellow portion of the spectrum (gray curve).



The absolute sensitivity to light also differs for the rod and cone photoreceptors. The rods are responsible for vision at dim light levels (for example, starlight and moonlight), while the cones respond to light only at higher levels (for example, normal room light and normal daylight).

The three types of cones account for humans' ability to distinguish lights of different wavelengths and thus to perceive colors. As an example, consider the response of a single class of photoreceptor (rods) with a single type of photopigment (rhodopsin) to lights of different wavelengths, as shown in Figure 16.24. If we shine a 500-nm light on a rod photoreceptor, we could

Figure 16.24
The response of a rod photoreceptor to light of various wavelengths. (A) The sensitivity of the rod photopigment, rhodopsin, to light of different wavelengths. Rhodopsin absorbs light best at 500 nm Ⓐ; at shorter wavelengths Ⓑ and longer wavelengths Ⓒ, it absorbs light less effectively. (B) The hyperpolarization produced in the rod by 100 photoisomerizations is shown on the right. This number of photoisomerizations of rhodopsin could be produced by a dim light at a wavelength of 500 nm Ⓐ, or by brighter lights at wavelengths Ⓑ or Ⓒ. All of these lights produce the same perception of brightness, because they generate the same size response in the rod. Thus, there is no basis for distinguishing lights of different wavelengths from lights of different intensities.


A
Sensitivity
Absorption spectrum of rhodopsin
Ⓑ
Ⓐ
Ⓒ
400
500
600
Wavelength (nm)
B
Dim 500-nm light
Ⓐ
100 photoisomerizations
Bright shorter-wavelength light
Ⓑ
100 photoisomerizations
Bright longer-wavelength light
Ⓒ
100 photoisomerizations
Time
Same response in rod photoreceptor
Rod E_m
Same perception of brightness

obtain a large light response with even a low light intensity, because rhodopsin best absorbs light with a 500-nm wavelength. If we use a shorter-wavelength light, we must increase its brightness to achieve the same level of response in the rod. Rhodopsin is less likely to absorb photons of light at the shorter wavelength (see Fig. 16.24A), and so a more intense light is required to obtain the same number of photoisomerizations in the rod outer segment. Similarly, if we use a light with a wavelength longer than 500 nm, a brighter light is also required to produce the requisite number of photoisomerizations. The size of the light response at all three wavelengths is the same, however. The nervous system cannot look at the output of the rod, then, and determine whether the rod light response was produced by a dim 500-nm light or by brighter lights of other wavelengths. In other words, brightness and wavelength are inherently confused if the visual system considers the output of a single type of photoreceptor, having a single type of photopigment. For this reason, humans cannot perceive color when the level of illumination is sufficiently dim that only our rod photoreceptors are active (for example, in moonlight or starlight).

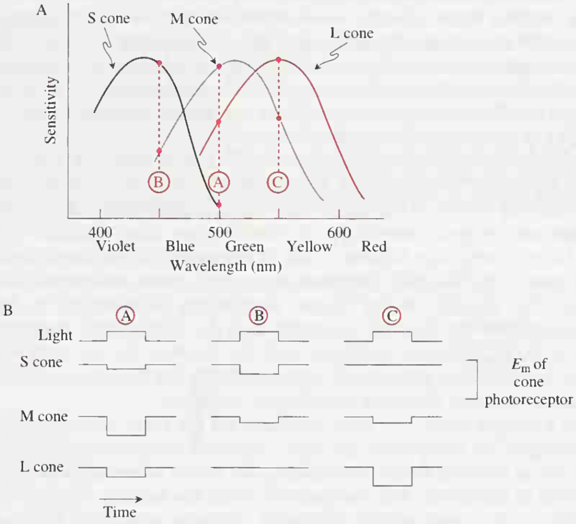
Now consider the response of the cone photoreceptor system to a similar set of light stimuli at three different wavelengths. Figure 16.25A shows the spectral sensitivity curves of the three types of cone photoreceptors. At the intermediate wavelength (wavelength A), M-cones are most sensitive, followed by L-cones, and then S-cones. Thus, the response to this wavelength will be greatest in the M-cones, intermediate in the L-cones, and smallest in the S-cones (Fig. 16.25B). At the shorter wavelength (wavelength B), the S-cones demonstrate the highest sensitivity and the largest light response, the M-cones have a smaller response, and the L-cones do not respond. Conversely, at the longer wavelength (wavelength C), the S-cones are insensitive, while the L-cones show the largest light response.

There is a unique pattern of light responses for the three cone types for each wavelength. By comparing the light responses originating from the cones, the visual nervous system can distinguish which wavelength of light was presented to the retina. This comparison forms the basis for the perception of color in the visual system. Normally, the light arriving at the eyes represents a mixture of different wavelengths, rather than a single wavelength. The visual system can then determine the relative contribution of light from different wavelengths by analyzing the strength of the neural signals originating from each type of cone photoreceptor.

Color-sensitive ganglion cells

In part, the comparison between signals coming from different types of cones occurs within the retina itself. Some types of ganglion cells do not respond well to white light (which consists of all wavelengths in the visual part of the spectrum). Instead, these cells respond best to light of a specific color. In keeping with the importance of spatial information in the visual system, such ganglion cells have spatially organized receptive fields. Like many other ganglion cells, the color-sensitive ganglion cells have center-surround receptive fields (Fig. 16.26). Illumination in the center of the receptive field produces the opposite effect to illumination in the surround regions. In the

Figure 16.25
The pattern of responses in the three types of cone photoreceptors provides the information necessary to distinguish lights of different wavelengths. (A) The absorption spectra of the three cone photopigments. Lights of wavelengths Ⓐ, Ⓑ, and Ⓒ are absorbed to different extents by the three photopigments. (B) Examples of responses of three cones to the wavelengths illustrated in A. At the middle wavelength, all three cones respond to the light, but the response is largest in the M-cone. At the shorter wavelength, the largest response arises in the S-cone. At the longer wavelength, the L-cones demonstrate the largest response.

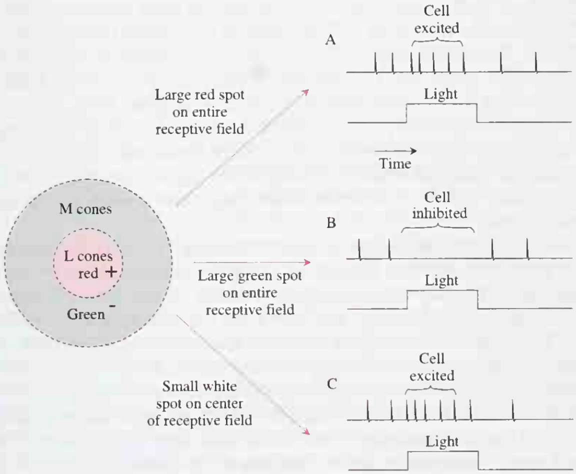


color-sensitive cells, the center and surround responses originate from different types of cone photoreceptors. Thus, the responses depend on the wavelength of light falling on the central region and the surround region of the receptive field.

Consider, for example, the ganglion-cell receptive field shown in Figure 16.26. The excitatory receptive-field center is mediated via L-cones, while the inhibitory surround region originates from M-cones. If a red light covers the entire receptive field of this neuron, the cell will be strongly excited (see Fig. 16.26A). The L-cones in the excitatory center of the receptive field are more sensitive to the red light than the M-cones in the inhibitory surround region (see, for example, Fig. 16.23), producing excitation of the ganglion cell. Conversely, if a green light covers the receptive field (see Fig. 16.26B), the M-cones of the inhibitory surround will be preferentially stimulated, resulting in inhibition of the ganglion cell. Therefore, this ganglion cell will be excited by red light and inhibited by green light.

There are many different varieties of such color-sensitive ganglion cells. Some ganglion cells have receptive fields with opposite organization from that illustrated in Figure 16.26—that is, with the surround portion of the receptive field originating from L-cones, and the center of the receptive field originating from M-cones. Such ganglion cells will be inhibited by a diffuse red light and excited by a diffuse green light. The ganglion cells that have opposing responses to red and green lights are called **red/green opponent ganglion cells.** The two varieties of red/green cells are red excitatory center, green inhibitory surround (as shown in Figure 16.26) and green excitatory center, red inhibitory surround. Other ganglion cells have receptive fields whose centers originate from S-cones and whose surrounds originate from M-cones, or vice versa. These **blue/yellow opponent ganglion cells** produce

Figure 16.26
An example of the receptive field of a color-sensitive ganglion cell. The concentric receptive field on the surface of the retina is shown in top view on the left. In this case, the excitatory center of the receptive field is formed by synaptic connections to L-cones, while the inhibitory surround region originates from M-cones. (A) A red spot that covers the receptive field will preferentially stimulate the L-cones and excite the ganglion cell. (B) A green spot that covers the receptive field preferentially affects the M-cones and inhibits the ganglion cell. (C) A white spot placed on the center of the receptive field also excites the ganglion cell and cannot be distinguished from a red stimulus.


A
Cell excited
Light
Time
Large red spot on entire receptive field
M cones
L cones red +
Green –
B
Cell inhibited
Light
Large green spot on entire receptive field
C
Cell excited
Light
Small white spot on center of receptive field

opposing responses to blue lights (affecting primarily S-cones) and yellow lights (affecting primarily M-cones). The two varieties of blue/yellow cells are blue excitatory center, yellow inhibitory surround and yellow excitatory center, blue inhibitory surround. Because both the center and the surround of all such ganglion cells derive from a single type of cone photoreceptor, color-sensitive cells of this type are called **single-opponent cells.**

Although the responses of these ganglion cells are sensitive to the wavelength of the illuminating light, they do not provide unambiguous information about stimulus color. Figure 16.26C shows how the output of the red-center ganglion cell fails to distinguish between a red stimulus and a white-light stimulus that covers only the center of the receptive field. The white light, which consists of photons of all visible wavelengths, stimulates the L-cones that generate the excitatory center response of the ganglion cell. Consequently, a small spot of white light on the receptive field center excites the ganglion cell in the same manner as a diffuse red light (see Fig. 16.26A). By examining the output of only this type of ganglion cell, the visual nervous system could not distinguish between the two types of stimuli. Clearly, information coming from other types of ganglion cell must be combined with information from these color-sensitive cells at higher levels in the visual system to resolve the ambiguity. In chapter 17, we will describe how this color information is further processed in the parts of the brain devoted to vision.

SUMMARY

The translation of light energy into electrical signals takes place through a process called phototransduction, which occurs in specialized neurons called photoreceptors. The photoreceptors are located in the retina at the back of the vertebrate eye. There are two classes of photoreceptors: rods, which function in dim light, and cones, which function in brighter light. Photons of light are absorbed by visual pigment molecules located in the photoreceptor cells. The pigment molecule of the rods is called rhodopsin. The pigment molecule is formed from the covalent linkage of the light-absorbing chromophore group, called retinal (or vitamin A aldehyde), and a large membrane protein, called opsin.

When retinal absorbs a photon of light, it undergoes a photoisomerization from a folded form (11-*cis* retinal) to a straight form (all-*trans* retinal). This isomerization triggers a conformation change in the opsin protein, revealing a cytoplasmic binding site for a GTP-binding protein called transducin. The activated rhodopsin catalyzes the replacement of GDP by GTP on transducin, thereby activating the G-protein. Transducin in turn activates a phosphodiesterase enzyme, which hydrolyzes cyclic GMP to GMP. Thus, absorption of light causes a decrease in the intracellular concentration of cyclic GMP in the photoreceptor. Cyclic GMP is an internal messenger that binds to and opens nonspecific cation channels in the plasma membrane of the photoreceptor cell. In darkness—when cyclic GMP levels are high—the channels are open and the photoreceptor is depolarized; in light—when cyclic GMP levels are low—the channels remain closed and the photoreceptor membrane potential is more negative. Thus, light hyperpolarizes the photoreceptor cells.

The photoreceptors release glutamate from synapses onto horizontal cells and bipolar cells. Glutamate release is higher in darkness, when the photoreceptors are depolarized. Horizontal cells are depolarized by glutamate, which opens nonspecific cation channels; as a result, horizontal cells hyperpolarize in response to illumination. The horizontal cells are lateral inhibitory interneurons, which release the neurotransmitter GABA.

Bipolar neurons produce two types of postsynaptic responses. Off-type bipolar neurons have glutamate-gated non-specific cation channels, depolarize in darkness, and hyperpolarize in response to light. On-type bipolar cells depolarize in response to illumination, as cyclic GMP-gated channels open. This latter action occurs because glutamate reduces cyclic GMP concentration in the bipolar neurons, via a GTP-binding protein and phosphodiesterase in a manner analogous to the phototransduction process in the photoreceptors. The receptive field of each bipolar neuron has a center-surround organization, with a central region where light either depolarizes the cell (on-type bipolar cells) or hyperpolarizes it (off-type bipolar cells) and a larger concentric region where light produces the opposite effect. This opposing effect from the surrounding portion of the receptive field is mediated via the lateral synapses made by the horizontal cells.

The bipolar cells carry light signals to the third-order neurons in the retina, known as amacrine cells and ganglion cells. The amacrine cells are lateral inhibitory interneurons that mediate lateral interactions analogous to those of the horizontal cells. The ganglion cells are the retina's output cells, and their outgoing axons form the optic nerve. Electrical signals in the ganglion cells are carried by action potentials; amacrine cells also make action potentials in response to depolarization. In the other retinal neurons (photoreceptors, horizontal cells, and bipolar cells), electrical signals are carried passively and action potentials are not involved.

Information about the color of incoming light originates in the cone photoreceptors, which contain photopigments that are sensitive to different parts of the visible spectrum. Humans possess three types of cones: the S-cones are most sensitive to short wavelengths (perceived as blue), the M-cones are sensitive to the middle wavelengths (perceived as green and yellow), and the L-cones are most sensitive to long wavelengths (the red part of the visible spectrum). Some types of ganglion cells have receptive fields that originate from particular cone types, rendering these cells sensitive to the wavelength of illumination. Such color-sensitive ganglion cells have center-surround receptive fields, but the center and surround regions originate from different types of cones. For this reason, lights in different parts of the visual spectrum produce opposing effects on the color-sensitive ganglion cell. For example, a red light might excite the cell, while a green light inhibits it.

17

The Visual System: Higher Visual Processing

In chapter 16, we learned how light is absorbed in the retina and converted into electrical signals. We also saw that the synaptic connections among the neurons in the retina are arranged to extract particular kinds of information about illumination that falls on the array of photoreceptors. This visual information is carried from the retina to the rest of the nervous system by the temporal patterns of action potentials in the axons of retinal ganglion cells, which make up the optic nerve. The ganglion cells do not report a simple point-by-point representation of the outputs of the photoreceptors. Instead, each ganglion cell is sensitive to particular spatial patterns of illumination, to the color of the light, or to other, more complex attributes of light stimuli. In other words, the ganglion cells are specialized to extract particular types of information about the visual world, which they then transmit to other parts of the visual system for analysis and construction of visual perceptions. The ganglion cells of various types form multiple, parallel information channels into the brain. In this chapter, we will turn our attention to the parts of the visual brain that are specialized to analyze object form, location, motion, and color based on the information provided by the retina in these parallel channels.

TARGETS OF THE RETINAL GANGLION CELLS IN THE BRAIN

The axons of the retinal ganglion cells project to multiple targets in the brain. In animals without a well-developed forebrain, the principal target is a part of the dorsal midbrain called the **optic tectum.** In mammals, the equivalent part of the brain is the **superior colliculus**, which helps integrate visual information with motor output in the neural systems that control eye movements (see chapter 12). Some retinal ganglion cells also send axons to the **suprachiasmatic nucleus**, which controls the entrainment of biological rhythms by the diurnal light cycle. As the large cerebral cortex emerged during mammalian evolution, these older visual areas of the brain were supplemented by another projection pathway for information leaving the eyes via the optic nerve: the **geniculostriate pathway**, which sends optic projections first to the **thalamus** and then from the thalamus to the **striate cortex.** In primates (including humans), this newer visual pathway has come to dominate in the processing of visual information, and large portions of the cerebral cortex are devoted to analysis of the neural outputs of the geniculostriate pathway.

The geniculostriate pathway is named after its two components: the visual relay station in the thalamus (the **lateral geniculate nucleus**) and the striate cortex. The striate cortex (the primary visual cortex) receives its name from the conspicuous stripe (or striation) that appears in the middle of the cortical layers; this stripe arises because the unusually large number of thalamic synaptic inputs to layer IV (the cortical layer that receives thalamic inputs; see chapter 11) makes this layer particularly prominent in the primary visual cortex. Under Brodmann's cortical numbering scheme (see chapter 11), the primary visual cortex is known as **area 17.** The approximate locations of the lateral geniculate nucleus and the primary visual cortex are shown for the human brain in Figure 17.1.

The optic nerves from the two eyes merge at the base of the brain, forming a structure called the **optic chiasm.** The axons of the retinal ganglion cells then separate again to form the two **optic tracts,** which project to the lateral geniculate nuclei on both sides of the brain. There, the axons of the ganglion cells end, making synaptic connections with the neurons of the lateral geniculate nucleus. The thalamic neurons in turn send their axons to the primary visual cortex, in the occipital lobe at the back of the brain.

Most of the primary visual cortex is hidden from view if we look at an intact human brain from the outside. Much of it is located on the most medial surface of the occipital lobe, within the midline infolding where the two cerebral hemispheres face one another. In addition, the primary visual cortex in each of the two occipital lobes forms a deep infolding at the rearmost pole of the brain, called the **calcarine fissure.**

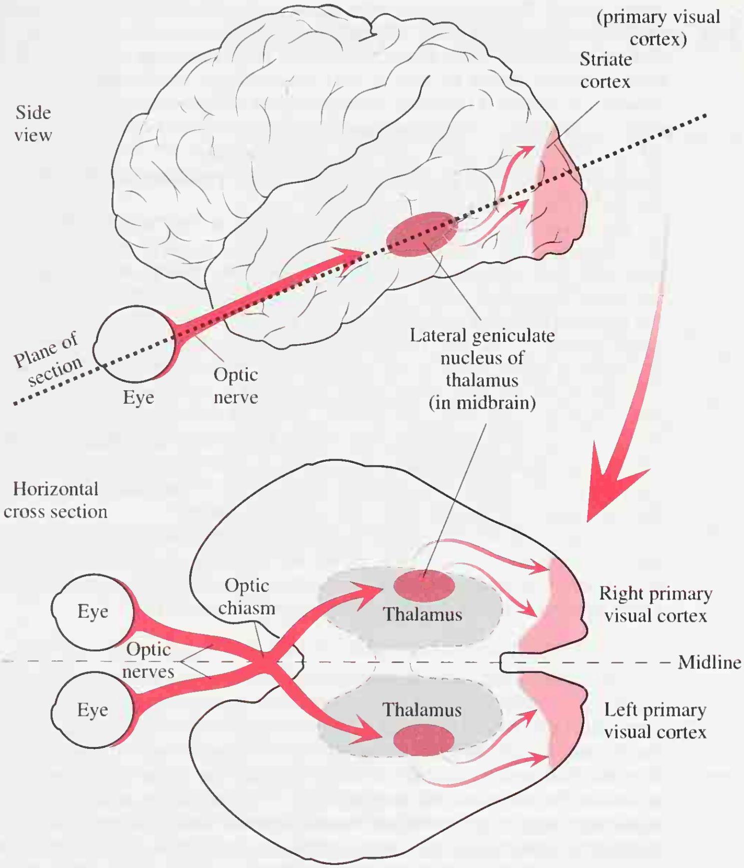
Another name for the primary visual cortex is **area V1**, which stands for visual cortical area number one. As we will see later, there are many other cortical areas in the primate brain concerned with the further processing of visual information that first reaches the cortex in area V1.

Organization of retinal inputs to the lateral geniculate nucleus

In many vertebrates, including fish and amphibians, the two eyes are located on the sides of the head and take in light from non-overlapping parts of the visual world, as shown in Figure 17.2A. The part of the visual world seen by the left eye is called the left **visual field,** and the part seen by the right eye is called the right visual field. In these animals, the axons of the ganglion cells from the two eyes cross completely at the optic chiasm, so that the right visual field projects to the left tectum and the left visual field projects to the right tectum (see Fig. 17.2A). In animals having both eyes in the front of the head, such as primates, the eyes overlap in their coverage of the visual world, so that the same visual stimulus appears simultaneously on both retinas (Fig. 17.2B). The result is **binocular vision.**

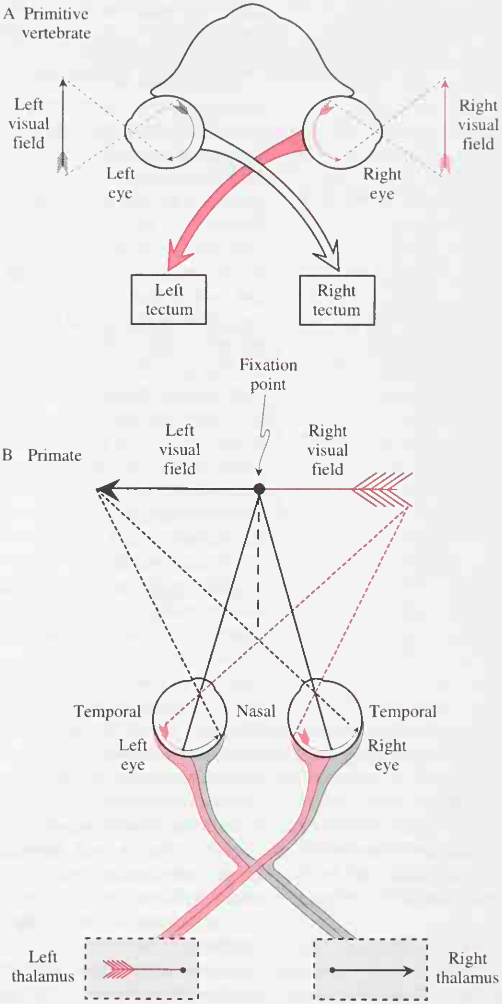
Although the visual world can still be divided into two visual fields for animals that have binocular vision, the left and right visual fields are defined with respect to the point of fixation of the two eyes (see Fig. 17.2B). Objects in the left and right visual fields will have images projected onto both retinas, but the optics of the eye dictate that light from the left visual field is directed

Figure 17.1
The anatomical organization of the geniculostriate visual pathway (red). (top) Side view. (bottom) Horizontal cross section in the plane shown above.



onto the **temporal retina** (toward the temples) of the right eye and onto the **nasal retina** (toward the nose) of the left eye. Conversely, light from the right visual field falls on the nasal retina of the right eye and the temporal retina of the left eye. The fixation point is always located on the **fovea** of the retina, the area with the highest density of photoreceptor cells and the best visual

Figure 17.2
Each half of the visual field projects to the opposite side of the brain. (A) In animals with laterally placed eyes, the left and right visual fields do not overlap, and the optic nerves from the two eyes cross completely at the midline. (B) In animals with frontally placed eyes, the left and right visual fields are represented in both eyes. To produce the correct separation of the two visual fields, the axons of ganglion cells in the nasal part of both retinas cross to the opposite side of the brain at the optic chiasm; the axons from the temporal retinas of both eyes remain on the same side of the brain.



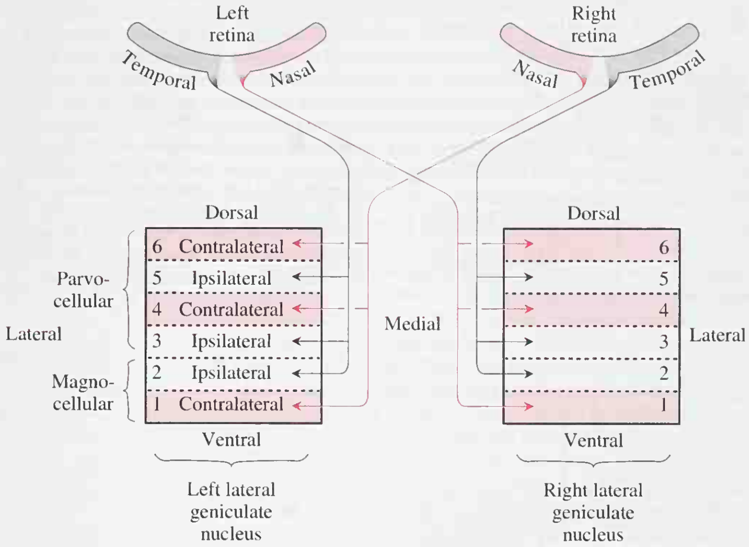
acuity. As with vertebrates that have the eyes placed laterally, the left visual field projects to the right side of the brain and the right visual field to the left side of the brain.

In the case of binocular vision, the projection pattern of the optic nerve axons required to separate the two visual fields is a bit more complicated than that encountered in vertebrates with laterally located eyes. This is illustrated in Figure 17.2B. The axons of the retinal ganglion cells sort themselves out at the optic chiasm according to the portion of the retina occupied by the ganglion cell. Ganglion cells in the temporal part of each retina send their axons to the same side of the brain, while the ganglion cells in the nasal part of each retina send their axons to the opposite side of the brain. As shown in Figure 17.2B, this projection pattern allows the left half of the visual field to be represented in the right thalamus and the right half of the visual field to be represented in the left thalamus. In reality, however, the dividing line between the temporal and the nasal retina is not as sharp as that shown in the figure. There is a narrow strip of retina, centered on the fovea, where the ganglion cells sort their axons randomly to either the ipsilateral or the contralateral side of the brain. That is, some ganglion cells in this central region behave as though they are "nasal" and some behave as though they are "temporal." Thus, the foveal region of the retina is actually represented on both sides of the brain, as indicated in the representations of the visual stimuli arriving at the left and right lateral geniculate nuclei in Figure 17.2B.

In addition to the coarse same-side/different-side sorting of the ganglion cell axons, there is also a specific ordering of the projections of optic nerve axons within each lateral geniculate nucleus. As shown schematically in Figure 17.3, each lateral geniculate nucleus is a laminated structure with distinct cellular layers. The number of layers varies somewhat in different species of mammals. In primates (including humans), six layers may be distinguished, numbered 1 through 6 from bottom (ventral) to top (dorsal). The two most ventral layers are further distinguished from the top four layers on the basis of the size of the neurons they contain. Neuronal cell bodies are larger in the bottom two layers, which are called the **magnocellular layers** (*magno* = "large"). The top four layers are called the **parvocellular layers** because their neurons have smaller cell bodies (*parvo* = "small"). As we will discuss shortly, the parvocellular and magnocellular layers are characterized by functional differences related to the types of visual information they relay.

Each layer in the lateral geniculate nucleus receives input from a particular eye. In other words, all of the thalamic neurons within a particular layer are **monocular**, even though the nucleus as a whole receives inputs from both eyes (see, for example, Fig. 17.2). Layers 2, 3, and 5 receive inputs from ganglion cells in the ipsilateral eye, while layers 1, 4, and 6 receive inputs from the contralateral eye (see Fig. 17.3). Thus, the inputs from the two eyes remain segregated and do not merge at the level of the thalamus. The receptive fields of the lateral geniculate neurons are thus confined to one eye or the other, depending on the layer of the nucleus in which the cell is found.

Figure 17.3
The lateral geniculate nucleus is organized into layers, each dedicated to a particular eye. Inputs from the contralateral eye are shown in red, and the layers of the contralateral eye layers appear in pink.



Synaptic circuitry of the lateral geniculate nucleus

Two general types of neurons are found in the lateral geniculate nucleus, and both types receive direct synaptic inputs from the retinal ganglion cells. The great majority (approximately three-fourths) of the neurons in the lateral geniculate nucleus are **projection neurons** (also called **relay neurons**), whose axons leave the thalamus and terminate in the primary visual cortex, in area 17 at the rearmost pole of the occipital lobe. These axons remain on the same side of the brain. As a result, the left half of the visual field is represented in the right primary visual cortex, and the right half of the visual field is represented in the left primary visual cortex.

The remaining one-fourth of the lateral geniculate neurons are **local interneurons**, which use the neurotransmitter GABA and make inhibitory synaptic connections onto nearby projection neurons within the lateral geniculate nucleus (Fig. 17.4A). The local interneurons provide lateral inhibition, analogous to the lateral interneurons encountered in our discussions of synaptic interactions in the somatosensory system (see chapter 15) and in the retina (see chapter 16). By adding another level of lateral inhibition within the thalamic relay nucleus, the lateral interneurons are thought to enhance the antagonism between the center region and the surround region

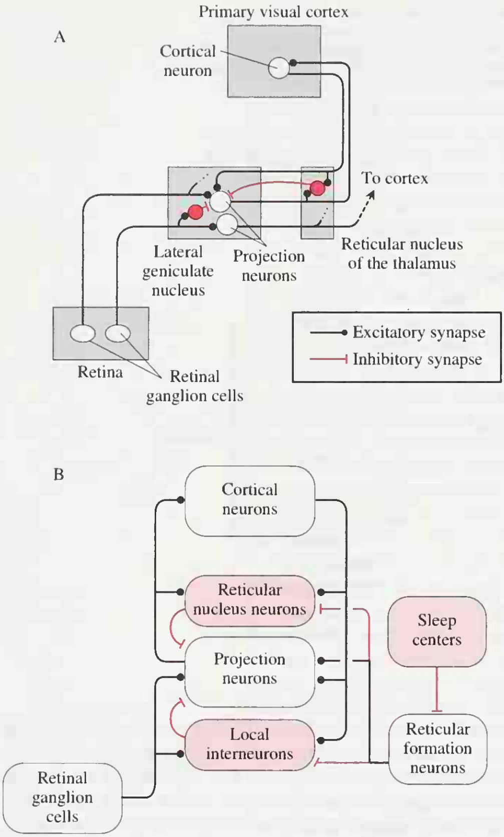


Figure 17.4
The synaptic circuitry of the lateral geniculate nucleus of the thalamus. (A) The axons of retinal ganglion cells make excitatory synapses within the lateral geniculate nucleus on projection neurons (white) and local inhibitory interneurons (red). The projection neurons send their axons to the primary visual cortex; they also send axon branches to inhibitory feedback neurons in the reticular nucleus of the thalamus. Cortical neurons make feedback synapses on both the neurons of the reticular nucleus and the projection neurons of the lateral geniculate nucleus.
(B) The synaptic circuitry shown in A is also influenced by neurons in the reticular formation that generate arousal. These neurons are in turn inhibited by brain centers that induce sleep.

of the receptive fields of the projection neurons in the lateral geniculate nucleus. The synaptic terminals of the ganglion cells apparently always make excitatory connections onto the projection neurons and local interneurons. Thus, the receptive fields of the projection neurons in the lateral geniculate nucleus are not fundamentally different from the receptive fields of the ganglion cells that connect to them. The receptive fields in the thalamus have a center-surround organization, and the sign of the response to illumination in the center and surround regions follows that of the ganglion cells sampled by the lateral geniculate neuron. In other words, on-center projection neurons are driven by on-center ganglion cells, and off-center projection neurons are driven by off-center ganglion cells.

From the discussion presented so far, the thalamus might be perceived as simply a relay station on the way to the cortex, collecting all types of sensory information and then distributing the outputs to the appropriate parts of the cerebral cortex for analysis and construction of perceptions. However, as shown in Figure 17.4, the synaptic interactions in the thalamus are actually more complex than this simple picture. In addition to the GABA-containing local interneurons mentioned above, other inhibitory interneurons are located just outside the thalamus in the **reticular nucleus of the thalamus**, which forms a shell surrounding the thalamic nuclei themselves. As the axons of the projection neurons pass through the reticular nucleus on their way to the visual cortex, they give off branches that make excitatory synaptic contacts with the inhibitory interneurons in the reticular nucleus. These interneurons send axons back to the projection neurons and make inhibitory feedback synapses. This negative feedback tends to oppose the relay of information from the thalamus to the cortex by reducing activity in the projection neurons.

Another important feedback loop that affects the activity of the projection neurons is also shown in Figure 17.4A. Some neurons in primary visual cortex, which is the target for the axons of the projection neurons, send axons back to the lateral geniculate nucleus, where they make excitatory synapses onto the projection neurons. This excitatory connection enhances the activity of the projection neurons, creating positive feedback for on-type light responses. In the off-pathway, in which illumination inhibits action potential activity, the level of activity in darkness will be enhanced by such corticothalamic excitatory synapses. In addition, as the axons descending from the cortex pass through the reticular nucleus of the thalamus, they send branches that make excitatory synapses onto the inhibitory interneurons of the reticular nucleus. By exciting the reticular nucleus neurons these synaptic connections indirectly inhibit the activity of the projection neurons. The net effect of the descending cortical axons on the projection neurons may, therefore, be either excitation or inhibition, depending on the relative strength of the excitation applied to the projection neurons and to the reticular nucleus neurons.

The cortical axons also target the local inhibitory interneurons within the lateral geniculate nucleus (for the sake of simplicity, Figure 17.4A does not show this synaptic connection). These connections provide another synaptic pathway by which cortical influences can affect both inhibitory light responses and excitatory light responses of projection neurons.

Figure 17.4B illustrates another reason to think that the thalamus is not just a passive relay station for sensory information on its way to the cortex. The balance between excitatory and inhibitory influences in the lateral geniculate nucleus is controlled by brain mechanisms that are involved in arousal and sleep. Neurons in the **reticular formation** of the midbrain and brainstem send axons to the thalamus, where they make synapses onto projection neurons, local interneurons, and neurons in the reticular nucleus of the thalamus. (Be careful to distinguish the reticular *nucleus* of the thalamus from the reticular *formation* of the midbrain and brainstem.) Recall that the reticular formation receives inputs from a variety of sensory sources and modulates spinal motor circuitry. It also controls the organism's overall level of arousal. During sleep, when the arousal level is at a minimum, the neurons of the reticular formation are inhibited (see Fig. 17.4B). At the thalamus, the projection neurons are excited by the reticular formation inputs, while the local interneurons within the lateral geniculate nucleus and the inhibitory neurons in the reticular nucleus are inhibited. By directly exciting the projection neurons and inhibiting the inhibitors of the projection neurons, the overall level of excitation in projection neurons is greatly enhanced. Thus, when the reticular formation is active, the relay of visual information from the thalamus to the cortex is enhanced. Conversely, during sleep, the inhibitory influences within the thalamus are maximal because the reticular formation is inactive, and the relay of sensory information to the cortex is not favored.

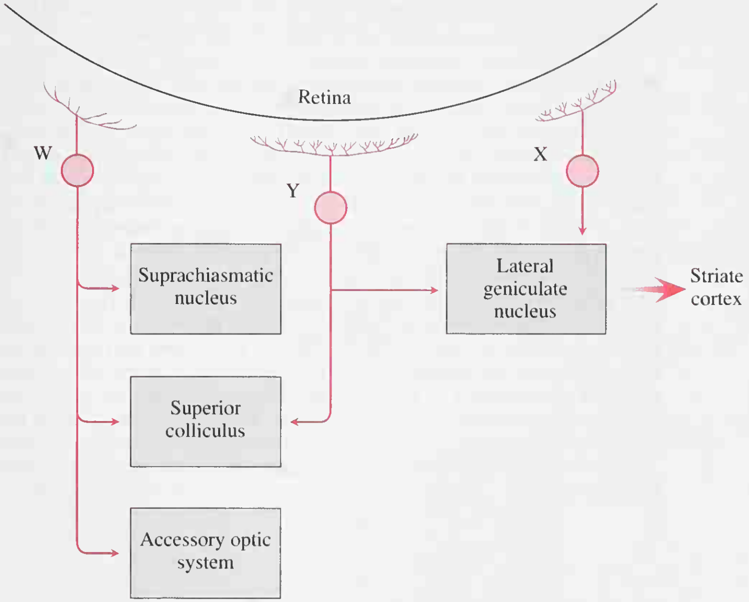
The inhibitory and excitatory synapses on the three types of thalamic neurons arise from branches of the axons of the same group of reticular formation neurons. The neurotransmitter released at both the inhibitory and the excitatory synapses is acetylcholine. Thus, as we saw in chapter 8, a neurotransmitter can be either excitatory or inhibitory, depending on what type of postsynaptic receptor it interacts with on the postsynaptic cell. In the case of the excitatory synapse from the reticular formation onto the lateral geniculate projection neurons, acetylcholine directly binds to and activates a ligand-gated ion channel that increases the sodium permeability of the postsynaptic neuron. In the case of the inhibitory synapses from the reticular formation neurons onto the local inhibitory interneurons and the reticular nucleus neurons, acetylcholine binds to a receptor that acts via G-proteins, indirectly opening potassium channels in the postsynaptic cell.

Different types of retinal ganglion cells project to different targets in the brain

Recall from chapter 16 that there are many different types of retinal ganglion cells, defined on the basis of their receptive fields and the kind of light stimulus to which they best respond. In broad terms, the many types of ganglion cells in mammalian retinas can be classified into three general categories: **X cells**, **Y cells**, and **W cells**. These categories are defined in part by the size of the cell body of the ganglion cell and by the dendritic branching pattern in the retina (Fig. 17.5). Y cells have the largest cell bodies and large dendritic fields; X cells have medium-size cell bodies and small, dense dendritic arbors; W cells have the smallest somata with widely spreading dendrites.

In addition, important functional differences distinguish the three types of cells. W cells are thought to represent a phylogenetically more ancient class of ganglion cells. In keeping with this notion, these cells send axons to the "older" parts of the visual nervous system, including the superior colliculus, the suprachiasmatic nucleus, and parts of the brainstem involved in controlling eye movements (the accessory optic system discussed in chapter 12). The W cells do not seem to participate in the "newer" geniculostriate pathway. The projection pattern for the W cells is summarized in Figure 17.5. As might be expected for such a diverse category, the W cells do not display a single type of light response that could be considered typical. Some W cells are selectively sensitive to moving stimuli, others are not; some W cells have center-surround receptive fields, others do not; and so on.

Figure 17.5
The three general classes of ganglion cell in the mammalian retina. The W cells represent a phylogenetically older class of ganglion cells whose axons project to the more primitive visual centers. The geniculostriate pathway originates from the X and Y cells. X cells are smaller than Y cells and have smaller dendritic and receptive fields.



Both X cells and Y cells have center-surround receptive fields. In keeping with the relative sizes of their dendritic trees, however, the Y cells have receptive fields that are three to four times larger than those of the X cells. As a result, the X cells are better suited for distinguishing closely spaced stimuli. X cells project exclusively to the lateral geniculate nucleus, while Y cells send axons to both the lateral geniculate nucleus and the superior colliculus. In addition, Y cells typically respond transiently to illumination and tend to prefer moving targets, while X cells produce a sustained response. In species in which color vision is highly developed (including primates), the X cells are sensitive to color, while the Y cells are not. Both categories include on-center and off-center ganglion cells.

It is important to recognize that every point in the retina is sampled in parallel by several different types of ganglion cell, each of which is looking for a different aspect of the visual stimulus. These parallel information paths are maintained at higher levels of analysis in the visual system, as the information passes from one stage to another. The X, Y, and W categories of ganglion cell were first described for the visual system of the cat, but functionally equivalent categories have been found in the retinas of other mammals (including primates) as well. In primates, the X cells are termed **P cells** (for parvocellular) and the Y cells are called **M cells** (for magnocellular). For simplicity, we will use the X and Y terminology in this book, but students should be aware that different terminology (and some functional differences) may be encountered when reading original research papers on the primate visual pathways.

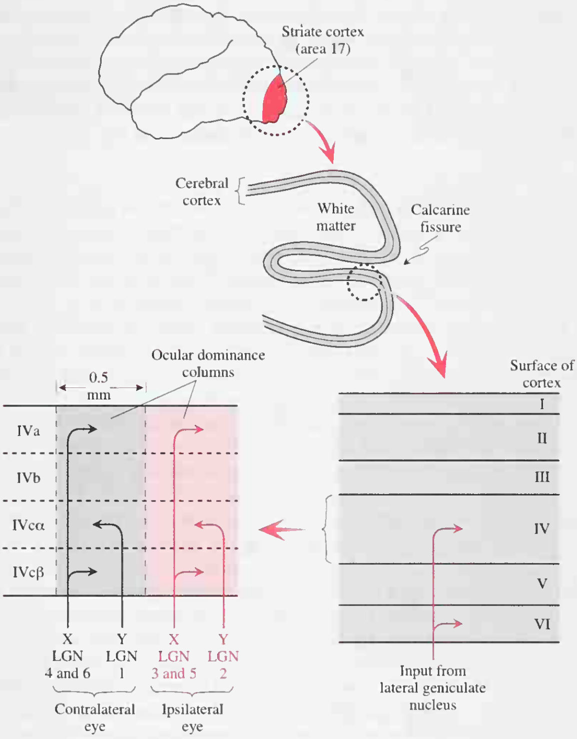
Perhaps the most significant reason for splitting the X and Y cells into different categories is that the projections from these two types of ganglion cell are segregated and connect with different sets of neurons in the lateral geniculate nucleus and the primary visual cortex. Thus, the visual system makes distinctions between these two pathways and the information they carry. In the lateral geniculate nucleus, each projection neuron receives input from either X cells or Y cells, but not both. Furthermore, the Y-cell inputs are sent only to layers 1 and 2 in the primate lateral geniculate nucleus. Recall that these layers are the magnocellular layers in primates. Thus, the largest ganglion cells (Y cells) project to the largest lateral geniculate neurons (magnocellular ganglion cells to magnocellular lateral geniculate cells). The layers also alternate in terms of the eye of origin of the retinal inputs. Thus, for the lateral geniculate nucleus on each side of the brain, all Y cells from the nasal retina of the contralateral eye project to layer 1, while all Y cells from the ipsilateral temporal retina project to layer 2. The parvocellular layers of the primate lateral geniculate nucleus receive inputs only from X cells (parvocellular ganglion cells to parvocellular lateral geniculate neurons). In this way, the layers of the lateral geniculate nucleus are organized to segregate not only the inputs from the two eyes, but also the X and Y pathways for visual information.

ORGANIZATION OF THE PRIMARY VISUAL CORTEX

The inputs to the striate cortex (Brodmann's area 17) from the lateral geniculate nucleus are also spatially organized with respect to the contralateral and ipsilateral eyes and with respect to the X and Y pathways. Recall from the discussion of the motor cortex in chapter 11 that the cerebral cortex is divided into six layers. As in the motor cortex, the arriving inputs from the thalamus terminate predominantly in layer IV of the primary visual cortex (Fig. 17.6). The unusually large thalamic input in the primary visual cortex makes layer IV thicker and more prominent than in other parts of cerebral cortex, as noted earlier. Indeed, layer IV is sufficiently thick in the primary visual cortex to warrant subdivision into four sublayers: IVa, IVb, IVcα, and IVcβ. These subdivisions and the origin of their inputs from the lateral geniculate nucleus are illustrated in Figure 17.6.

The inputs from the ipsilateral and contralateral eyes are segregated into specific dorsal/ventral layers of the lateral geniculate nucleus. In the cortex,

Figure 17.6
The location and laminar organization of the primary visual cortex (the striate cortex). Like other areas of the cerebral cortex, the primary visual cortex has six layers. Layer IV is further divided into four sublayers. The inputs derived from the ipsilateral and contralateral eyes are spatially separated into vertically oriented columns, called the ocular dominance columns. The inputs from the X- and Y-cell pathways in the lateral geniculate nucleus are spatially segregated within an ocular dominance column.



the inputs from these geniculate layers remain segregated, so that inputs coming from the contralateral and ipsilateral eyes do not overlap. The cortical neurons receiving inputs from a particular eye are arranged in vertically oriented columns, called **ocular dominance columns**, that are approximately 0.5 mm wide (see Fig. 17.6). The contralateral-eye and ipsilateral-eye columns alternate throughout primary visual cortex. Thus, on each side of the brain, the ipsilateral-eye columns receive inputs from layers 2, 3, and 5 of the lateral geniculate nucleus on that side of the brain, while the contralateral-eye columns receive inputs from layers 1, 4, and 6 (see Fig. 17.6).

The axons coming from the X and Y pathways in the lateral geniculate nucleus terminate in different sublayers of cortical layer IV (see Fig. 17.6). The incoming Y axons make synaptic connections in sublayer IVcα; the incoming X axons project to sublayer IVa and to IVcβ. This arrangement holds for both the axons carrying information from the contralateral eye and the axons from the ipsilateral eye, in their respective ocular dominance columns. The incoming axons from the lateral geniculate nucleus make synapses onto stellate cells (described in chapter 11) in layer IV. In addition, the axons of both the X and Y pathways branch as they pass through layer VI of the primary visual cortex. These branches make synapses onto pyramidal neurons in layer VI, which are the source of the feedback axons that return to the lateral geniculate nucleus from the cortex (see Fig. 17.4).

Receptive fields of cortical neurons

Like the retinal ganglion cells and the neurons of the lateral geniculate nucleus, the stellate cells in layer IV of the primary visual cortex have concentric center-surround receptive fields with either excitatory or inhibitory centers. Above and below layer IV, however, most neurons have receptive fields that differ in fundamental ways from the center-surround organization.

Figure 17.7 shows an example of a commonly observed receptive field shape for cortical neurons. In the example, the central excitatory region is surrounded by an inhibitory region, but both are elongated rather than circular, as in retinal ganglion cells and lateral geniculate neurons. The best stimulus for this neuron would be a bar of light just wide enough to cover the central excitatory region and oriented parallel to the long axis of the receptive field. If the bar is rotated so that it is perpendicular to the long axis of the receptive field, it fails to excite the neuron (see Fig. 17.7). Similarly, a circular spot of light would not be a particularly effective stimulus for this cell. Thus, cortical neurons of this type show the greatest sensitivity to a bright line or a bar of light with a specific orientation.

A receptive field of this type can be constructed if an appropriate series of on-center stellate cells from layer IV make excitatory synapses onto the cortical neuron in the manner shown in Figure 17.7. When off-center cells are used as the building blocks instead of on-center cells, they produce a cortical cell most sensitive to a dark line of a particular orientation on a bright background. The receptive fields of the retinal ganglion cells can be envisioned as building blocks for the construction of more complex receptive fields, after the outputs of the ganglion cells are relayed through the thalamus and the stellate cells of layer IV of the cortex. There are several variations of rectangular receptive fields in the primary visual cortex, involving different receptive field sizes, or antagonistic regions flanking only one side of the excitatory region, or other arrangements. As a group, these orientation-sensitive cortical neurons were called **simple cells** by their discoverers, David Hubel and Torsten Wiesel, who won the Nobel Prize for their studies of visual cortical neurons and their response properties. If we sample a variety of locations in the primary visual

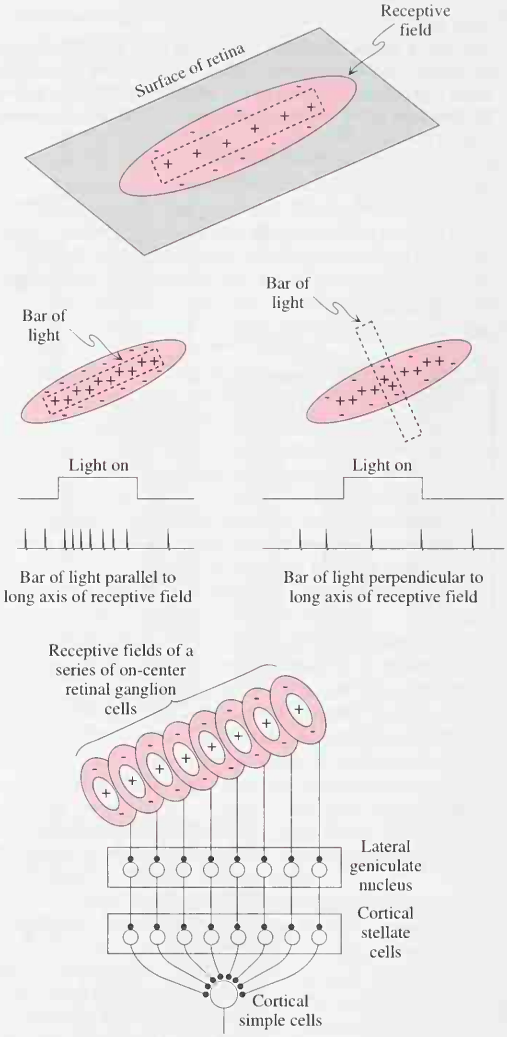
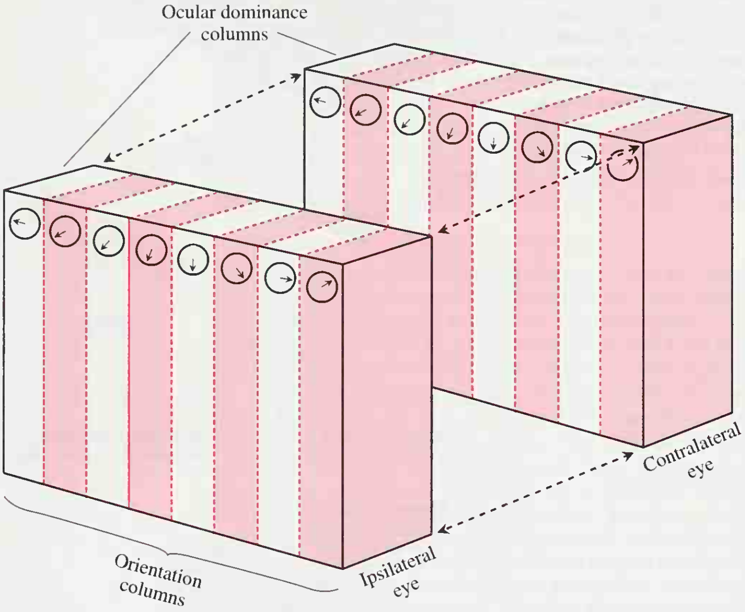

Receptive field
Surface of retina
Bar of light
Bar of light
Light on
Light on
Bar of light parallel to long axis of receptive field
Bar of light perpendicular to long axis of receptive field
Receptive fields of a series of on-center retinal ganglion cells
Lateral geniculate nucleus
Cortical stellate cells
Cortical simple cells

Figure 17.7
The receptive field of a cortical neuron that is most sensitive to a long bar or line of light with a particular orientation. The shape of the receptive field on the surface of the retina is shown at the top. If a bar of light is oriented so that it coincides with the long, narrow excitatory center of the receptive field, the cell is strongly excited. If the bar of light is rotated so that its long axis does not coincide with the long axis of the receptive field, the cell fails to respond. A receptive field of this type can be constructed by combining an appropriate set of center-surround receptive fields (bottom).

Figure 17.8
Cells with a similar orientation preferences form vertical columns in the primary visual cortex. The successive orientation columns within an ocular dominance column have slightly different preferred orientations, indicated by the arrows on the clock faces in each column. The differences in the directions of the arrows in successive columns are exaggerated here for illustrative purposes.



cortex, we would encounter simple cells with receptive fields covering all parts of the retinal surface and having all possible orientations.

Like the inputs from the two eyes, the orientation-sensitive neurons are arranged into vertical columns in the primary visual cortex. The arrangement of the **orientation columns** is shown in Figure 17.8. Within an orientation column, all simple cells have receptive fields with a similar orientation preference, but slightly different retinal locations. In the adjacent ocular dominance column from the opposite eye, the receptive fields of simple cells also have a similar orientation, but the cells are driven more strongly by the other eye. The simple cells within an ocular dominance column are driven more strongly by the eye of that column, but are also typically sensitive to illumination placed in the other eye. The locations of the receptive fields on the two retinas precisely coincide, so that each simple cell that receives input from the two eyes is driven binocularly by correctly oriented bars of light (or dark) at a particular position in the visual field. Because the incoming lateral geniculate axons project exclusively to a single ocular dominance column, the binocular responses of the simple cells must arise from cortico-cortical connections within the primary visual cortex.

Staying within an ocular dominance column and moving to successive orientation columns, the preferred orientation of simple cells moves progressively around the clock (see Fig. 17.8). The cortical surface in primary visual cortex comprises a two-dimensional array of columns, with the ocular dominance columns forming one axis of the array and the orientation columns forming the other axis. Thus, the map of the retinal surface created by the circular receptive fields of the retinal ganglion cells is transformed into a map of **orientation-selective line detectors** in the primary visual cortex. Each point in the visual field is covered by simple cells of all orientations; similarly, among the simple cells of a particular orientation, all positions in the visual field are covered.

In addition to the simple cells, Hubel and Wiesel described cortical cells with more complex response properties, which they called **complex cells** and **hypercomplex cells.** Like simple cells, complex cells are sensitive to the orientation of edges and lines. They have much larger receptive fields than simple cells and show greater variation in their response characteristics. These cortical neurons are commonly excited by a dark or a light bar or by an edge between light and dark regions placed anywhere in the receptive field, provided that the stimulus has the correct orientation. Complex cells of this type signal stimulus *orientation,* independent of stimulus *location* (within broad limits). The orientation-sensitive cells constitute the building blocks of a cortical system that analyzes the form or shape of a visual stimulus.

In some cases, the response of complex cells is greatest when an edge of the correct orientation moves through the receptive field in one direction, while movement of an edge in the opposite direction produces inhibition. These motion-sensitive neurons likely represent a separate analysis subsystem, concerned with detecting visual motion and specifying the direction of motion (discussed later as part of our examination of higher-order visual areas of the cortex). Hubel and Wiesel suggested that the response properties of complex cells could be produced by excitatory synaptic inputs from an appropriate group of orientation-sensitive simple cells to the complex cells, just as simple cells could be constructed from the combination of the appropriate center-surround receptive fields of stellate cells.

Hypercomplex cells resemble complex cells, except for one restriction: the bar or edge must not extend beyond the boundaries of the receptive field. In other words, hypercomplex cells are stimulated best by lines of a particular orientation and particular *length.* According to Hubel and Wiesel's theory, receptive fields like those of hypercomplex cells could result if the neuron receives excitatory and inhibitory connections from groups of complex cells.

These studies of receptive field properties of cortical neurons suggest how information about the orientation and length of the borders that define objects in the visual world might be extracted from lower-level data provided by retinal ganglion cells and lateral geniculate neurons. Two important and mutually complementary principles of cortical information processing emerge from this theory. First, features of the visual stimulus are extracted by a **hierarchical arrangement** of neurons whose receptive fields are constructed by the combinations of receptive fields of lower-level neurons in the hierarchy. Second, at each position on the retina, the "testing" of the visual stimulus for lines of particular orientation and length occurs **in parallel** for all possible orientations and lengths that the visual system can distinguish. Each position on the retina is represented many times in the visual cortex, so that many different simple cells (and hence, complex and hypercomplex cells) are simultaneously examining the same part of the visual world. Thus, **information processing in the visual cortex is both hierarchical and parallel: hierarchical within an orientation system, and parallel across orientation systems.** This principle is likely to apply not only in the visual cortex but in all parts of the cortex, including other sensory systems, motor systems, and cortical areas involved in much more complex processes.

Color-sensitive cells in the primary visual cortex

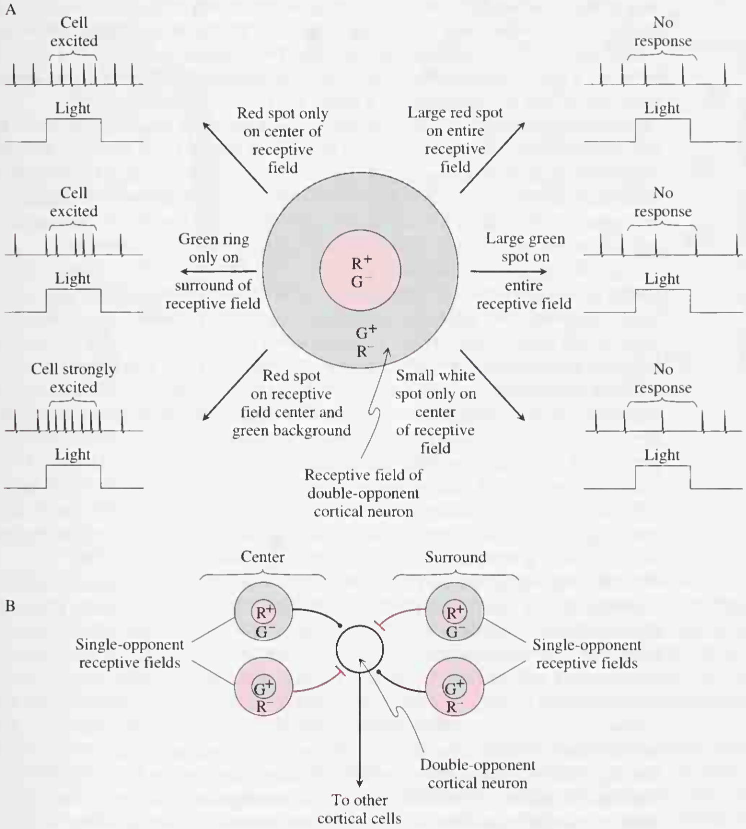
Another parallel information-processing pathway in the primary visual cortex focuses on analyzing the color of visual stimuli. In chapter 16, we discussed the responses of single-opponent, color-sensitive retinal ganglion cells. In the receptive fields of these cells, the center and surround regions originate from different types of cone photoreceptors. However, the color-sensitive ganglion cells cannot distinguish unambiguously between colored lights and white light that covers only part of the receptive field (see Fig. 16.26 on page 399).

These constraints also apply to the lateral geniculate nucleus, where the color-sensitive projection neurons have the same receptive field organization as that found in the ganglion cells. At the level of the cortex, however, the color-sensitive cells have receptive fields that differ in a subtle but important way from the receptive fields of the single-opponent cells. The response of a color-sensitive cortical neuron to various types of illumination is shown in Figure 17.9A. Unlike with the single-opponent cells, color opponency appears *within* the center and surround of the receptive field, as well as *between* the center and surround. Cells with receptive fields of this type are called **double-opponent, color-sensitive cells.** The example in Figure 17.9 illustrates a red/green double-opponent cell.

Opponent responses within both the center and surround of the receptive field allow the cortical cells to respond in a specific way to colored stimuli, without being confused by white lights. To see why this is true, consider the response pattern to stimuli that produce either excitation or inhibition of single-opponent cells (see, for example, Fig. 16.26 on page 399). A large red spot that covers the receptive field of the cortical cell produces no response because the superimposed excitation from the center and the inhibition from the surround cancel each other. This type of stimulus strongly excites a single-opponent cell (see Fig. 16.26). A large green spot that covers the receptive field inhibits a single-opponent cell, but has no effect on the double-opponent cell shown in Figure 17.9A because the light simultaneously produces inhibition from the center and excitation from the surround of the double-opponent receptive field. Similarly, a white light will not be an effective stimulus (see Fig. 17.9A) because white light would affect the

Figure 17.9

The response properties of a double-opponent, color-sensitive neuron in the primary visual cortex. (A) The receptive field is shown in the center, with responses to various types of stimuli arrayed around the outside. (See the text for a full description of the responses.) The best excitatory response is observed with a red spot of light on a green background (lower right). (B) Synaptic circuitry that could produce a double-opponent, color-sensitive neuron from appropriate combinations of single-opponent neurons.


A
Cell excited
Light
Red spot only on center of receptive field
Large red spot on entire receptive field
No response
Light
Cell excited
Light
Green ring only on surround of receptive field
R+
G−
G+
R−
Large green spot on entire receptive field
No response
Light
Cell strongly excited
Light
Red spot on receptive field center and green background
Small white spot only on center of receptive field
No response
Light
Receptive field of double-opponent cortical neuron
B
Center
Surround
R+
G−
G+
R−
R+
G−
G+
R−
Single-opponent receptive fields
Single-opponent receptive fields
Double-opponent cortical neuron
To other cortical cells

red-sensitive and green-sensitive mechanisms equally; thus, it would produce both excitation and inhibition of the double-opponent cell, even when restricted to the center of the receptive field. In a single-opponent cell, a white light restricted to the excitatory part of the receptive field produces strong excitation, causing the cell to confuse white and colored lights.

Now consider the response of a double-opponent cell to particular combinations of red and green lights (see Fig. 17.9A). A red spot of light restricted to the center of the receptive field would excite the cell. Similarly, a green ring of light falling only on the surround of the receptive field (excluding the center) would effectively excite the cell. The strongest excitatory response would occur with a combination of these two stimuli, such as a red spot of light on a green background. The strongest inhibition of the double-opponent cell would be produced by a green spot on a red background.

Several varieties of double-opponent, color-sensitive neurons are found in the visual cortex. Some are red/green cells (as in Figure 17.9), but with the opposite effects of red and green lights in the center and surround of the receptive field (that is, green excitation and red inhibition in the center, red excitation and green inhibition in the surround). Likewise, some double-opponent neurons are sensitive to yellow and blue lights, rather than red and green.

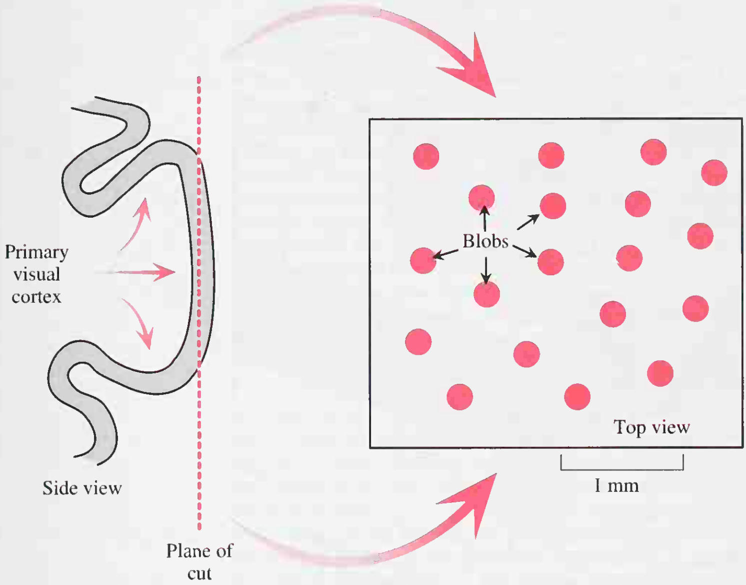
Double-opponent color-sensitive neurons can be created in the visual cortex by simple synaptic connections from incoming axons of single-opponent, color-sensitive projection cells arriving from the lateral geniculate nucleus. A cell with receptive field properties like that in Figure 17.9A could arise from the synaptic arrangement illustrated in Figure 17.9B. The central portion of the double-opponent cell's receptive field is formed by the combination of excitatory connections from red on-center single-opponent cells and inhibitory connections from green on-center single-opponent cells. In the surround portion of the receptive field, the connections are reversed (excitatory from green on-center and inhibitory from red on-center single-opponent cells). With this synaptic arrangement, red light on the receptive field center and green light on the receptive field surround would produce the strongest excitation, in keeping with the response properties shown in Figure 17.9A.

The color-sensitive cortical cells form a functionally distinct analysis pathway in the cortex, operating in parallel with the orientation pathway discussed previously. Color-sensitive cortical cells are also spatially segregated from the orientation-sensitive cells. Groups of color-sensitive neurons are interspersed among the orientation columns in a semi-regular array of vertically oriented columns called blobs. Figure 17.10 shows schematically the appearance of this array of blobs when the primary visual cortex of the primate brain is sliced parallel to the cortical surface and then viewed from the top. Although the blobs are found above and below layer IV, they are excluded from layer IV itself. The overall arrangement of the ocular dominance columns, the orientation columns, and the color-sensitive blob regions is shown in Figure 17.11.

The blobs in the primary visual cortex were first identified by anatomical characteristics rather than on functional grounds. When the cortex is stained to reveal the location of cells rich in the mitochondrial enzyme, cytochrome oxidase, the blobs are selectively stained. Therefore, the neurons in the blob

Figure 17.10

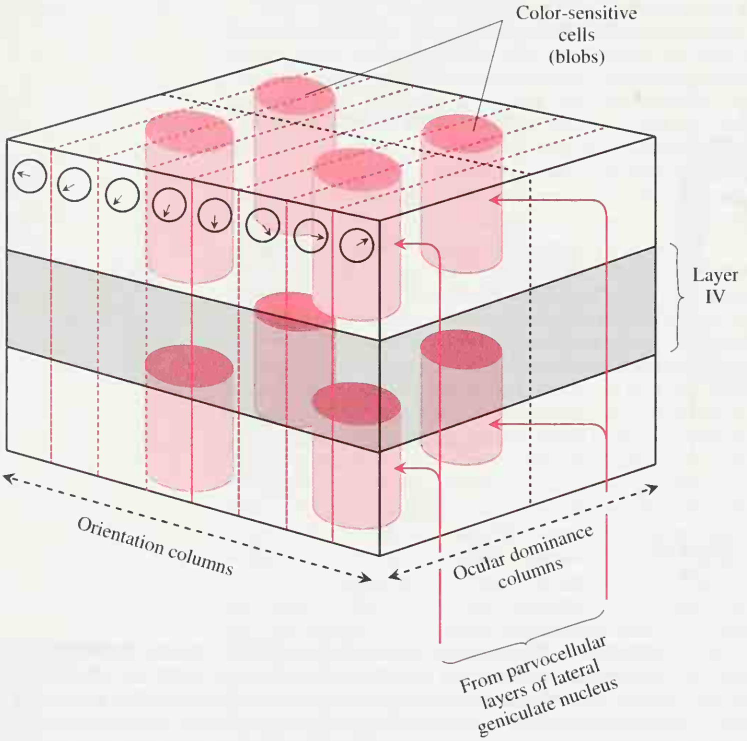
Color-sensitive neurons are localized in the primary visual cortex within blobs revealed by staining for cytochrome oxidase, a mitochondrial enzyme. The plane of a section parallel to the cortical surface is shown on the left, and a top view of the resulting section is shown on the right.



regions are capable of sustaining high metabolic activity. Physiological experiments have revealed that the cells within the blobs are color-sensitive cells. The relative importance of color in visual information processing in primates (including humans) is presumably reflected in an increased amount of action potential activity in the color-sensitive cells and thus a greater requirement for metabolic energy to sustain the transmembrane ionic gradients (see chapters 3 and 4).

The color-sensitive cells within the blobs receive direct inputs from the lateral geniculate nucleus, independent of the primary lateral geniculate projection into layer IV of the cortex. In primates, the color-sensitive retinal ganglion cells are X cells that project to the parvocellular layers of the lateral geniculate nucleus. Therefore, the color pathway in the primary visual cortex receives its inputs from the parvocellular layers (layers 3–6) of the lateral geniculate nucleus. In animals with well-developed color vision, the color-sensitive blob system is one of the principal cortical targets of the parvocellular pathway from the lateral geniculate nucleus.

Figure 17.11
The blobs form columns interspersed among the orientation columns and ocular dominance columns of the primary visual cortex. The blobs are found in all layers except layer IV. The inputs to the blobs come from the parvocellular layers of the lateral geniculate nucleus.


Color-sensitive cells (blobs)
Layer IV
Orientation columns
Ocular dominance columns
From parvocellular layers of lateral geniculate nucleus

HIGHER-ORDER VISUAL CORTICAL REGIONS

The primary visual cortex (area V1) supports multiple analysis pathways, operating in parallel, that analyze each point on the retina for different stimulus properties, including line length and orientation, object color, and motion. These functionally distinct pathways are also anatomically distinct. From area V1, the results of each parallel analysis system are passed to selected higher-order cortical areas for further processing of specific stimulus attributes. Ultimately, these separate stimulus attributes must be merged to form an integrated view of the visual world. From our own visual experience, we know that the nervous system is capable of constructing elaborate and highly integrated visual perceptions of the world around us.

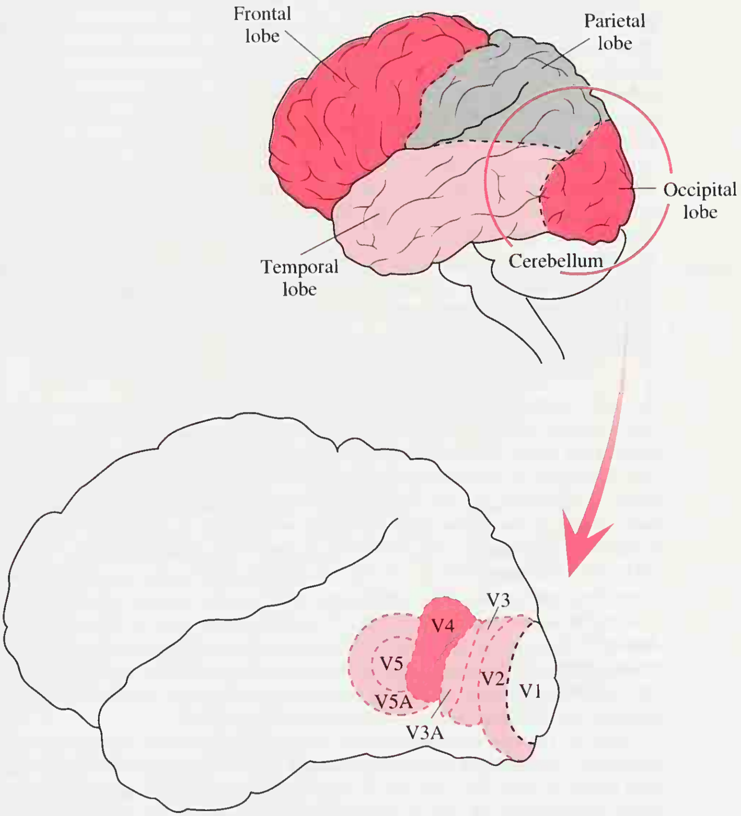
Although neurobiologists do not yet understand how these integrated perceptions arise, at least some clues about the higher-order cortical circuitry involved in analyzing the specific aspects of visual stimuli have begun to emerge. In primates, large portions of the cerebral cortex are devoted to these visual tasks, including parts of cortex that were once classified as "association" cortex because no clearly defined sensory or motor function could be attached to them. A great deal of the association cortex is now known to constitute part of the visual system in the primate brain. In keeping with the principles of combined hierarchical and parallel processing found in the primary visual cortex, these higher-order cortical regions show a hierarchical arrangement, but different types of visual analysis are carried out in parallel fashion in several cortical regions. We will begin by examining the anatomical layout and the interconnections of these higher-order visual areas, before turning to the visual responses of the neurons in some of the best-studied higher centers.

Anatomical arrangement of non-striate visual cortical regions

As noted earlier, the primary visual cortex is located at the rearmost pole of the occipital cortex. The higher-order visual cortical regions form a series of progressive rings of cortex as we move anteriorly through the occipital lobe into the posterior part of the temporal lobe. This is illustrated for the primate brain in Figure 17.12. The higher-order areas are numbered V2 through V5 successively as we move from posterior to anterior. In addition, area V3 is subdivided into areas V3 and V3A, and area V5 is subdivided into V5 and V5A. With the exception of area V4, the higher-order areas are buried mostly or entirely within the deep infoldings (sulci) of the cortical surface and are not visible on the external surface of the brain (indicated in Figure 17.12 by dashed lines marking the border between areas and by pink coloration). The three-dimensional relationship between the areas and their positions within the infoldings can be better appreciated by examining the horizontal cut through the visual cortical areas shown in Figure 17.13.

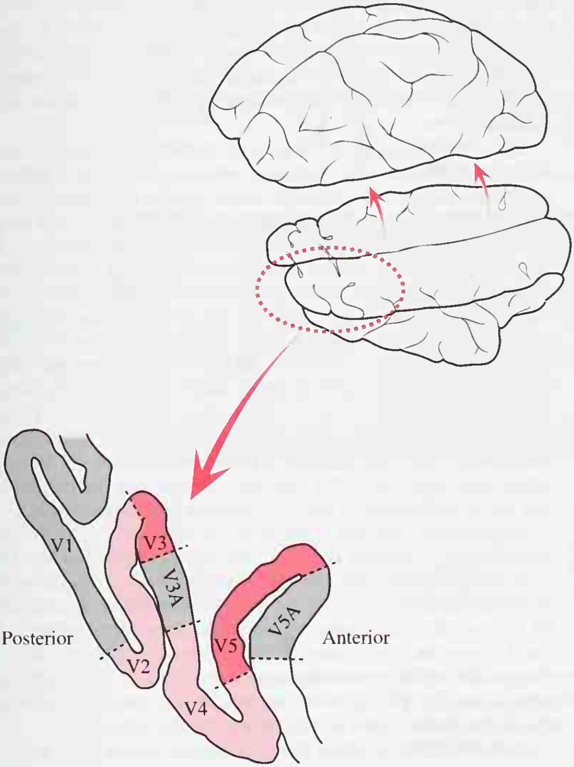
Area V2 receives extensive inputs from cortical neurons of area V1. Consequently, the multiple maps of the retinal surface represented in area V1 are also found in area V2. Area V2 is organized into spatially segregated functional subdivisions of cells that handle different aspects of visual stimuli, in a manner analogous to the organization of area V1. Also like area V1, the functional subdivisions of area V2 are revealed anatomically by cytochrome oxidase staining. In the case of area V2, there is a regularly repeating pattern of **stripes** of neurons rich in cytochrome oxidase, presumably corresponding to groups of neurons with high metabolic activity and thus high neuronal activity during visual analysis. The stripes run vertically from the cortical surface to the underlying white matter, as shown in Figure 17.14. The stripes are separated from each other by regions where the neurons have relatively

Figure 17.12
The location of the higher-order visual cortical areas in the occipital and temporal lobes of the primate brain. The dashed lines indicate areas hidden from external view within infoldings of the cortical surface.



little cytochrome oxidase, called the **interstripe** region. Stripes come in two thicknesses, called—not surprisingly—**thin stripes** and **thick stripes**. These bands occur in strict order—thin stripe, interstripe, thick stripe, interstripe, thin stripe, and so on—with the pattern repeating throughout area V2 (see Fig. 17.14).

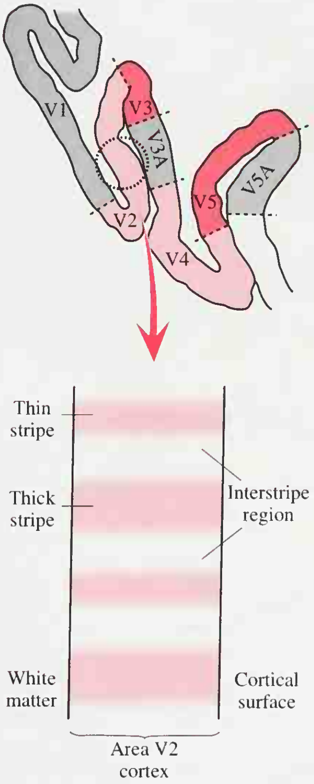
Figure 17.13
The locations of the higher-order visual cortical areas revealed by a horizontal section through the primate brain.



Functional connections from area V1 to area V2

Figure 17.15 summarizes the functional connections made by the different portions of area V2. The thin stripes in area V2 receive inputs from the cells in the blobs of area V1—that is, from the color-sensitive cells in the primary visual cortex. In turn, the cells in the thin stripes send axons to area V4, which is involved in color vision. Therefore, the pathway from the blobs of V1 to the thin stripes of V2 to area V4 can be thought of as a neural system specialized for the analysis of color of visual stimuli. The thick stripes in area

Figure 17.14
In area V2, staining for cytochrome oxidase reveals vertically oriented thick and thin stripes.



V2 receive synaptic connections from orientation-selective neurons in area V1, as described earlier. The thick stripes also receive inputs from the motion-sensitive neurons of area V1. Thus, the neurons in the thick stripes make up part of neural circuits that analyze object shape and detect and analyze motion. The orientation-selective neurons of the thick stripes send axons to area V3, which further analyzes object shape. In contrast, the motion-sensitive neurons of the thick stripes project to area V5, which analyzes object motion independent of object form, as we will describe below.

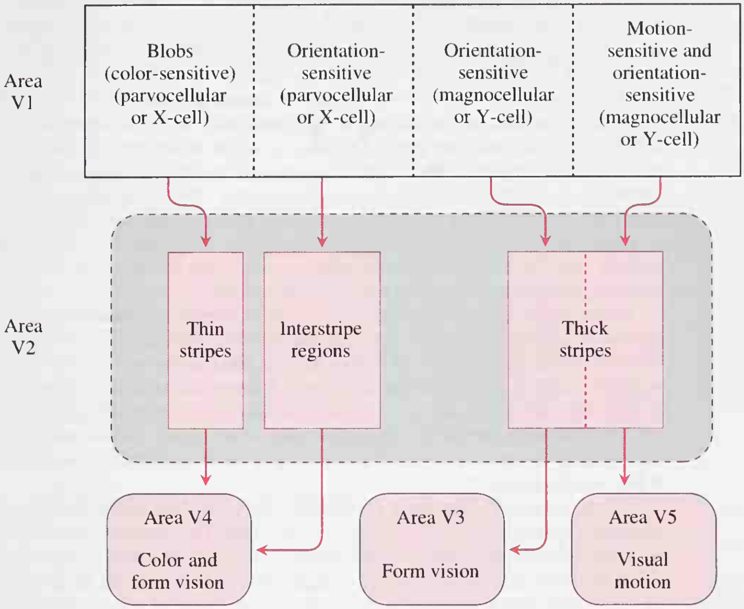
The interstripe regions of area V2 receive inputs from orientation-selective neurons of primary visual cortex, as do the thick stripes (see Fig. 17.15). The thick stripes receive their orientation-sensitive connections from V1 regions that are part of the magnocellular (or Y-cell) pathway, while the interstripes receive their orientation-sensitive connections from V1 regions that are part of the parvocellular (or X-cell) pathway. Recall that in the retina, the Y ganglion cells (the origin of the primate magnocellular pathway) have large receptive fields and thus low spatial resolution. Conversely, the X cells (the origin of the primate parvocellular pathway) have small receptive fields and thus high spatial resolution. As a result, the shape-analysis pathway that passes through the thick stripes in area V2 is best suited to crude object recognition and approximate spatial localization of objects within the visual field. The pathway through the interstripes in area V2 is more likely to be involved with fine form analysis.

In keeping with the separation of the magnocellular and parvocellular pathways through area V1 and into area V2, the interstripe regions and the thick stripes project to different higher-order targets: area V4 for the interstripe neurons and area V3 for the thick-stripe neurons. As might be expected given that area V4 receives inputs from both the color-sensitive cells in the thin stripes and the orientation-sensitive cells of the interstripe regions (see Fig. 17.15), some neurons in area V4 are sensitive to the orientation of lines or bars of a particular color.

It is tempting to think that the cortical visual areas form a linear hierarchy, with V1 projecting to V2 and V2 feeding the specialized higher areas. In reality, however, the pattern of interconnections is more complex. Area V1 sends outputs directly to the cortical regions specialized for motion and form, bypassing area V2; it also makes indirect connections to those same areas via area V2. In addition, intracortical connections from areas V3, V4, and V5 feed back to the "lower-order" areas V1 and V2. The precise function of these interconnections has not been established, but the anatomical interconnections are clearly complex—as might be expected for neuronal circuits performing analysis and synthesis as complicated as that involved in visual perception.

In many respects, area V2 mirrors the organization observed in area V1. The orientation- and color-sensitive cells are spatially segregated, and the

Figure 17.15
The organization of connections from area V1 to area V2 and from area V2 to the specialized cortical visual areas.


Area V1
Blobs (color-sensitive) (parvocellular or X-cell)
Orientation-sensitive (parvocellular or X-cell)
Orientation-sensitive (magnocellular or Y-cell)
Motion-sensitive and orientation-sensitive (magnocellular or Y-cell)
Area V2
Thin stripes
Interstripe regions
Thick stripes
Area V4
Color and form vision
Area V3
Form vision
Area V5
Visual motion

magnocellular and parvocellular subsystems are separately represented. Thus, the scheme of multiple, parallel subsystems—each concerned with a different aspect of the visual world—is observed in area V2, as it was in area V1. The principal difference is that the proportion of cells with hypercomplex receptive field properties is higher in area V2 than in area V1.

At the next level of cortical processing, cells have receptive fields that differ in fundamental ways from those encountered in area V1 and area V2. As an example, we will consider the properties of cells in area V5, which are specialized for processing of information about the motion of visual stimuli.

Detection and analysis of visual motion: area V5

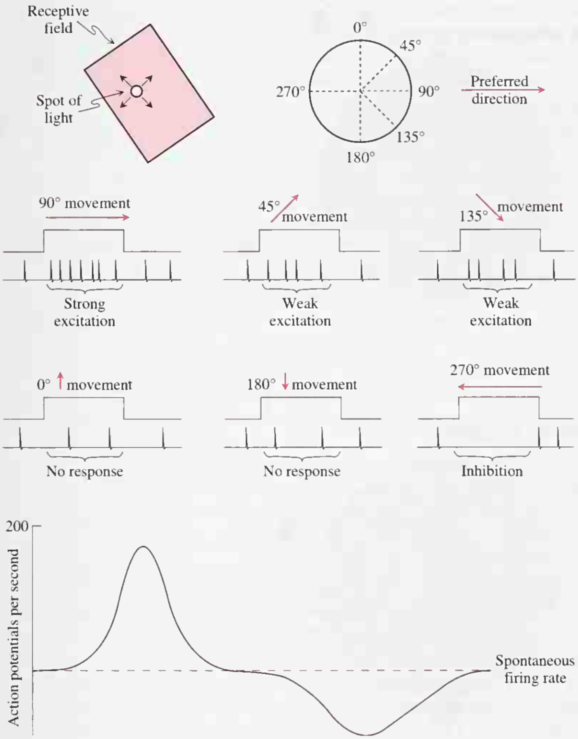
One of the most important tasks of the visual system is to detect moving objects and determine their direction of motion. A moving object may represent food or an approaching predator, both of which are visual stimuli with obvious implications for survival. The analysis of movement also provides an excellent example of how different aspects of visual information processing may be separated into spatially distinct cortical areas, each specialized for a particular type of information. In the case of motion, the specialized cortical area is area V5, which is also known as **area MT** (*m*iddle *t*emporal area). Area V5 is buried within a sulcus in the posterior and superior part of the temporal lobe (see Figs. 17.12 and 17.13). The cells in this area commonly have large receptive fields, but they do not respond well to steady illumination. If a spot of light is moved anywhere within the receptive field, however, it generates a brisk response. An example of how a cortical neuron in area V5 responds to a moving stimulus is shown in Figure 17.16. Each cell has a strong preference for movement in a particular direction. Movement in other directions produces weaker excitation, while movement in the opposite direction produces inhibition. For each cell in area V5, it is possible to construct a direction preference curve like that shown in Figure 17.16. Among the population of motion-sensitive cells in area V5, all possible direction preferences and all possible receptive field locations are represented. The cells in area V5 respond equally well to lights of different wavelengths—that is, the cells are not color-sensitive.

Interestingly, the neurons in area V5 are evidently specialized to signal *movement,* independent of the *shape* of the moving stimulus. How can shape be separated from movement? Under normal conditions, movement will be associated with a particular form or shape, because the stimulus arises from a particular object moving in the visual world. Thus, movement and shape will not normally constitute separable traits of an object. Nevertheless, the cells in area V5 are able to respond briskly to a moving stimulus, even when it has no shape.

To see how experimenters produce a shapeless, but moving stimulus, consider the diagrams in Figure 17.17. In this case, the stimulus consists of a large number of dots of light, which remain on for a brief time and then turn off again (only a small number of dots are shown in the figure for the sake of clarity). At the next instant, the dots turn on again at a new, randomly determined position within the field of view. The result is a randomly scintillating field, similar to the "snow" on a TV screen that is not tuned to a broadcasting channel. When the dots move to a random position (see Fig. 17.17A), a human observer does not perceive any motion from the stimulus. We can induce a perception of motion, however, by making a small change in the stimulus conditions. At each successive instant in time, a small percentage of the dots move in a particular direction, rather than to a random position (see Fig. 17.17B). Thus, at each point in time, a small fraction of the dots undergoes a correlated shift in direction. At the next instant, a different subset of dots undergoes a correlated shift in the same direction. This process is repeated at each successive instant in time for the duration of the stimulation. Although the stimulus still lacks a discernible overall pattern and human observers report that it has no "shape," the dots nevertheless produce a strong perception of "movement" in the direction of the correlated shift. In other words, motion and shape have been effectively separated by this laboratory-generated stimulus.

The larger the fraction of dots undergoing the correlated shift, the easier a human observer can detect the direction of motion and report it reliably.

Figure 17.16
Responses of a motion-sensitive neuron in area V5. The preferred direction of motion for this example is from left to right in the horizontal plane, which corresponds to 90° on the circular direction diagram (top). When a spot of light moves through the receptive field in this direction, it strongly excites the cell. Movement in the opposite direction produces inhibition. The directional preference of this example cell is shown in the bottom diagram.



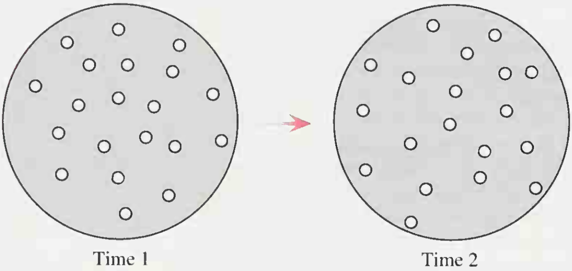
When the percentage of correlated dots falls below approximately 4%, human and monkey observers can no longer detect the direction of motion.

The movement-sensitive cells in area V5 also give strong responses to the random-dot stimulus illustrated in Figure 17.17B, provided that the direction of correlated movement agrees with the cell's preferred direction. Area V5, then, contains neurons that respond to motion, even when the

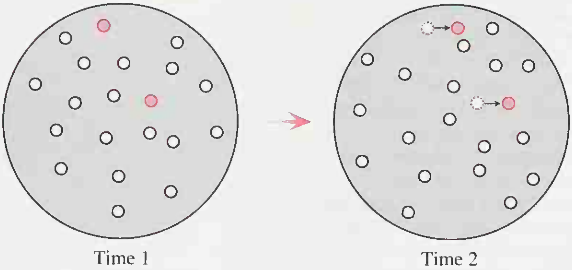
Figure 17.17

A random-dot stimulus can be used to produce a perception of movement, without an accompanying object shape or form. (A) A set of white dots is illuminated on a dark background at time 1. At time 2, the dots are extinguished and reappear at new, random positions. This stimulus produces no overall perception of motion. (B) Most of the stimulus mirrors that seen in A, but two dots (red) undergo a shift in a specified direction, rather than a random shift in position. This type of stimulus produces a perception of drifting motion from left to right.

A Random position of dots: No perception of motion



B 10% of dots move in specified direction: Perception of motion



moving stimulus is “shapeless.” Furthermore, the responses of neurons from area V5 to the random-dot stimuli can account quantitatively for the motion perceptions of the intact animal. For example, the neurons fail to detect motion if the percentage of correlated dots is lower than 4%—the same percentage necessary to produce a behavioral response in the observer. This finding suggests that the output of the motion-sensitive neurons in area V5 determines the animal's perceptual performance in detecting visual motion.

Neurobiologists have also tested the role of area V5 in motion perception by placing a small stimulating electrode within the cortex of area V5 in an awake monkey. Weak electrical stimulation was then applied to artificially activate a small group of neurons that have a particular directional preference. If the monkey was viewing a random-dot stimulus, electrical stimulation biased the monkey's perceptual performance toward the direction of motion favored by the stimulated neurons. In other words, the monkey behaved as though it saw a moving stimulus when area V5 was electrically stimulated. This finding provided further evidence that the neurons of area V5 are uniquely responsible for determining the perception of visual motion.

It is interesting that one cortical target for the outputs of the motion-sensitive cells of area V5 is the **lateral intraparietal area**, which we encountered in our discussion of the oculomotor system in chapter 12. An important goal of the oculomotor system is to move the eyes so that the fovea coincides with the position of a moving object, and then to track the moving target by means of appropriate eye movements. The information provided by the motion analysis system in area V5 is likely to be an important aspect of the sensorimotor integration carried out in the lateral intraparietal area, which correctly positions the eyes to bring the moving object to the foveal region of the retina.

SUMMARY

The axons of the retinal ganglion cells form the optic nerves, which merge at the base of the brain at the optic chiasm. At the chiasm, the axons coming from ganglion cells in the nasal half of each retina cross to the opposite side of the brain; axons coming from ganglion cells in the temporal half of each retina remain on the same side of the brain. As a result, the left half of the visual field (nasal retina from the ipsilateral eye, temporal retina from the contralateral eye) is represented in the right half of the brain, while the right half of the visual field is represented in the left half of the brain.

The synaptic targets of the retinal ganglion cells in the brain include the optic tectum and, in mammals, the lateral geniculate nucleus of the thalamus. From the thalamus, visual information is relayed to the primary visual cortex (also called area V1 or the striate cortex). The lateral geniculate nucleus acts as a gate that controls passage of visual information from the retina to the visual cortex. The ability of the thalamic relay cells to transmit the visual information is governed by neurons in the reticular formation that are activated when the animal is aroused.

In the lateral geniculate nucleus, the projection neurons that send their axons to the cortex have receptive fields resembling those of the retinal ganglion cells—that is, they have a center-surround organization. In the primary visual cortex, however, a variety of different receptive fields are observed. Many neurons in area V1 are best stimulated by a bar or line of light of a particular orientation. These orientation-selective cortical neurons help detect the edges that define the borders of objects in the visual world. Some cortical neurons are motion-sensitive, requiring that the light of a particular orientation be moving in a particular direction. Other cortical neurons are color-sensitive, responding best to light of a particular wavelength.

The primary visual cortex is organized into a two-dimensional array of functionally defined columns of cells that extend from the cortical surface to the underlying white matter. Ocular dominance columns form one dimension of the array; these columns receive inputs preferentially from either the contralateral or ipsilateral eye in an alternating pattern. Orientation columns make up the other dimension of the array. All of the orientation-selective cells within an orientation column are best stimulated by lines of light with the same orientation, but falling on slightly different retinal locations. Within the primary visual cortex, each point on the retinal surface is examined in parallel by a group of orientation-selective neurons whose preferred orientations cover all directions. Similarly, each point on the retina is examined simultaneously by motion-sensitive neurons whose preferred directions of movement cover all possibilities. The primary visual cortex thus carries out in parallel an analysis of the visual field for a wide variety of aspects of visual stimuli, including line orientation, direction of movement, and object color.

There is also a hierarchical arrangement of information processing within the cortical visual system. For example, the orientation-selective neurons in the primary visual cortex are used as building blocks to construct cells with more complex receptive fields. Some of these more complex cells require that lines of light must have a specific length and a particular orientation. In this way, cortical neurons with more complex properties are constructed by various combinations of synaptic inputs from cells with simpler receptive field properties.

In addition, the information from the primary visual cortex is transmitted to higher-order cortical areas for further processing of specialized information. Area V2, which is found just anterior to the primary visual cortex (area V1), receives inputs from area V1. Area V2 includes subdivisions devoted to the further processing of object form, object color, and object motion. Both area V1 and area V2 also project to more specialized areas that are found in progressively more anterior portions of the occipital lobe and the posterior part of the temporal lobe of the cortex. Area V4 is specialized for color vision, area V3 for analysis of object shape, and area V5 for detection of motion.

18

Hearing and Other Vibration Senses

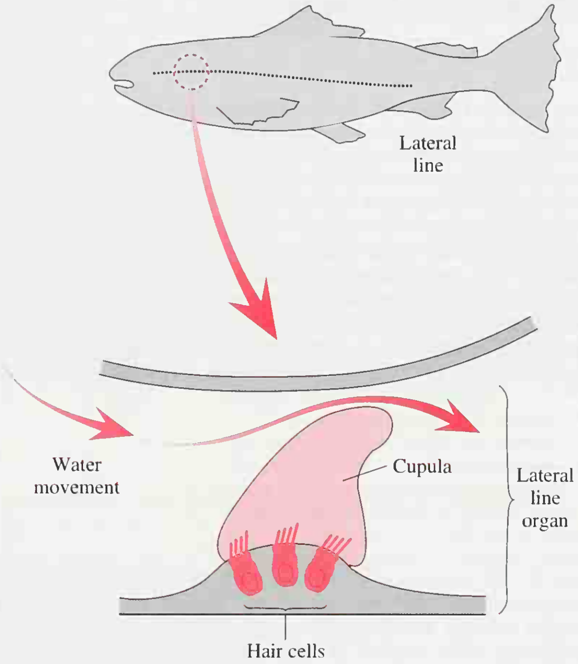
Chapters 16 and 17 focused on vision, one of the important distance senses used by organisms to sense objects in the environment from afar. In this chapter, we will examine another major sensory mechanism that allows animals to gather information about the environment without having to come into direct contact with objects. In this case, the physical energy used by the sensory system is mechanical vibration of the medium in which the organism is immersed. For terrestrial animals, that medium is the air; for aquatic animals, it is water. The human sensation produced by vibration of the air is called hearing. We will begin by examining the properties of the sensory receptors that are sensitive to the mechanical vibrations. We then describe the brain mechanisms that analyze the information provided by those sensory receptors, concentrating on the sense of hearing in mammals.

MECHANORECEPTORS OF VIBRATION SENSES: HAIR CELLS

Movements of both animate and inanimate objects in either air or water produce vibrations that propagate through the medium for distances that depend on the strength and frequency of the vibration as well as on the physical properties of the medium. When the vibration reaches the relevant sensory organ of the receiving animal, the mechanical energy of the vibration must be translated into an electrical signal, as in any sensory transduction process.

The mechanoreceptors for the vibration senses are **hair cells**, which we encountered in our discussion of the vestibular system in chapter 12. As an example of a vibration receptor organ, we will consider the **lateral line organ** (Fig. 18.1). Many aquatic vertebrates possess some variant of this organ, which is used to detect motion of the water around the animal's body. The sensory hair cells are located within pits or tubes in the skin, through which water flows. The moving water displaces a gelatinous body (called the **cupula**, just as in the vestibular apparatus) that projects into the pit or tube (see Fig. 18.1). The hair-like cilia of the hair cells in the organ are embedded in the cupola, whose motions deflect the cilia. As with the vestibular hair cells (see chapter 12), these deflections change the hair cell's membrane potential. In the next section, we will consider the mechanism

Figure 18.1
The structure of a lateral line organ. Within the lateral line, fluid movements deflect the cupula (pink). The ciliary bundles of the sensory hair cells (red) are embedded in the cupula.

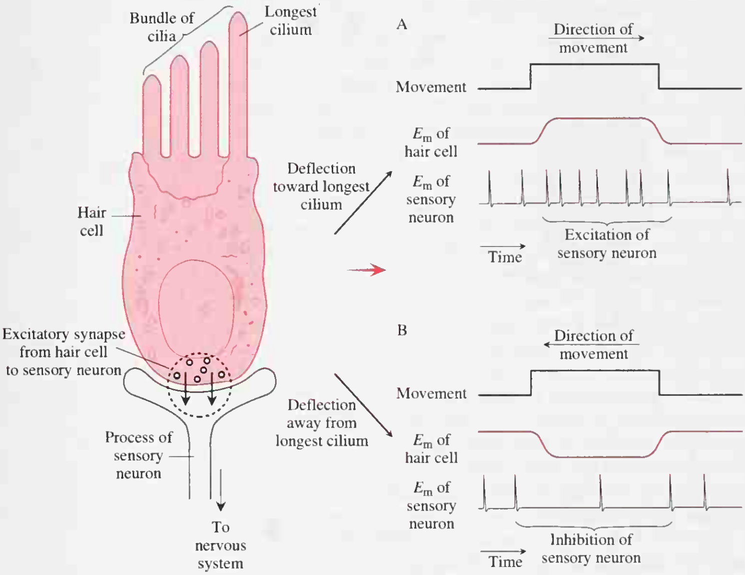


by which the movements of the cilia are translated into electrical signals, a process called **mechanosensory transduction.**

Mechanosensory transduction in hair cells

The cilia of the hair cell form a bundle at the top of the cell (shown in cross section in Figure 18.2). The cilia are not all the same length, however, but increase progressively in length as we move from one side of the bundle to the other. When the bundle is deflected toward the longest cilium, the hair cell depolarizes (see Fig. 18.2A). The depolarization increases the release of excitatory neurotransmitter at the synaptic connection between the hair cell and the sensory neuron that contacts it. As a result, the rate of action potential firing in the sensory neuron increases for this direction of move-

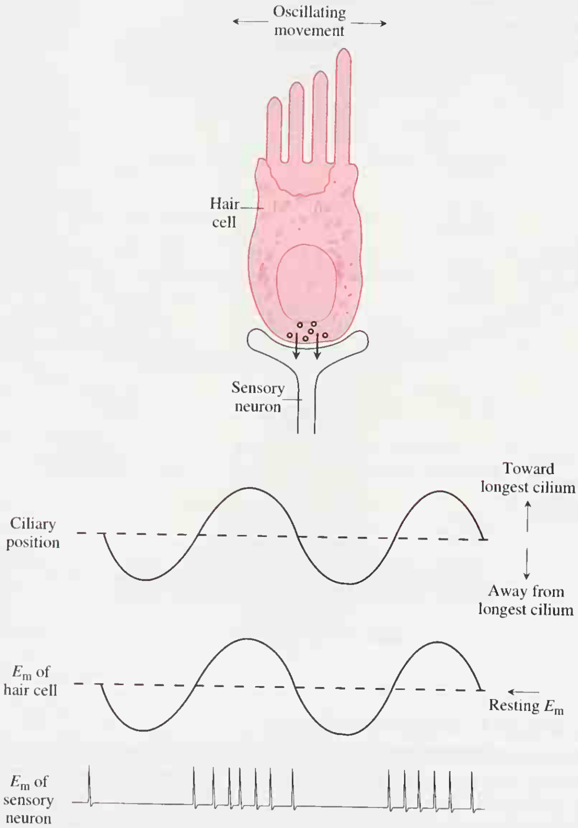
Figure 18.2
The electrical response of a hair cell and its sensory neuron to deflections of the bundle of cilia. The hair cell produces graded changes in the membrane potential in response to movement of the cilia and makes an excitatory synapse onto the process of the sensory neuron. (A) When the ciliary bundle is deflected toward the longest cilium (to the right in the diagram), the hair cell depolarizes and the excitation of the sensory neuron increases. (B) When the ciliary bundle is deflected away from the longest cilium (to the left), the hair cell hyperpolarizes, less excitatory transmitter is released, and the sensory neuron fires action potentials less frequently.



ment. When the bundle is deflected in the opposite direction, away from the longest cilium, the hair cell hyperpolarizes (see Fig. 18.2B). The release of excitatory transmitter from the hair cell decreases in response to this hyperpolarization, and the rate of action potential firing in the sensory neuron falls below the resting level. Thus, in response to movements of the cilia, the hair cell produces graded changes in membrane potential, which are then translated into changes in firing frequency of action potentials in the sensory neuron.

What would happen if the cilia moved back and forth, first toward and then away from the longest cilium? This situation is depicted in Figure 18.3. Vibration of the water flowing over the cupula would produce oscillating

Figure 18.3
Oscillatory motion of the ciliary bundle produces oscillating changes in the membrane potential in the hair cell. These oscillatory changes are reflected in bursts of action potential in the sensory neuron; these bursts occur with the same periodicity as the oscillating stimulus.



stimulation of this type. The hair cell would respond to such a stimulus with oscillating changes in membrane potential, tracking the position of the ciliary bundle. Coinciding with each depolarizing phase in the hair cell, the sensory neuron would fire a burst of action potentials. During each hyperpolarizing phase in the hair cell, the sensory neuron would be silent. Thus, the nervous system receives a series of repetitive bursts of action potentials from the sensory neuron, with the interval between bursts being determined by the frequency of the vibrating stimulus. If the frequency of the vibration increases, the duration of each burst of action potentials and the interval between successive bursts will become shorter. The nervous system can therefore obtain information about the frequency of a vibrating stimulus applied to the lateral line organ by analyzing the temporal pattern of action potential activity in the sensory neuron. This encoding mechanism works best, however, for low-frequency vibrations like those produced by the swimming motions of a nearby fish (predator, prey, or mate). In the case of mammalian sound perception, the relevant frequencies of oscillation are often much higher, and other mechanisms of encoding the frequency of a stimulus are required. We will describe these mechanisms later in this chapter, when we discuss the mammalian auditory organ.

Mechanically sensitive ion channels in hair cell cilia

The changes in the hair cell's membrane potential in response to cilia movements are caused by changes in the ionic permeability of the hair cell membrane induced by deflection of the cilia. The mechanism thought to underlie the change in permeability is illustrated in Figure 18.4. The cilia in the bundle are tethered together near their tips by fine filaments that extend from each cilium to the next taller one in the bundle. These filaments behave like little springs. In the resting state (see Fig. 18.4A), the springs are slightly stretched, transmitting tension to each anchor point on adjacent cilia. This tension influences the opening of mechanosensitive ion channels in the cilia. In the figure, this state is indicated by small trap doors that are directly connected to the tethering filaments. Because of the resting tension, some of the channels remain open even when the bundle assumes a neutral, upright position. The mechanically sensitive channels are cation channels that allow positive charges to enter the cilia, depolarizing the hair cell.

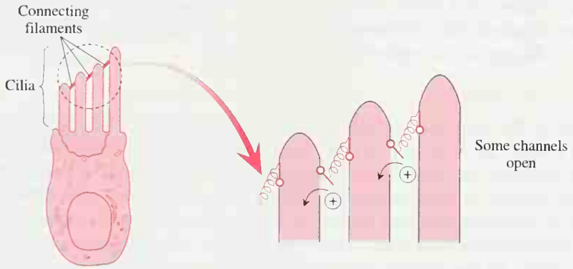
Consider what happens when the bundle is deflected. Despite the name "hair cell," which implies flexibility, the cilia are stiff and rigid (resembling the wires of a wire brush rather than the bristles of a paint brush). Therefore, the length of each cilium remains fixed during deflection, and the cilia slide past one another. You can easily construct a simple mechanical analogy of the cilia's behavior. Hold two pencils of slightly different lengths together vertically, with their eraser ends contacting a flat surface, such as a table top. While maintaining the contact point with the table top, move the tips of the pencils (still keeping them together) first toward the longer pencil, then toward the shorter pencil. Note how they slide past one another during the movement and how the distance between the tips becomes longer and shorter as you move them back and forth. This is illustrated for the cilia of the hair cell in Figures 18.4B and 18.4C.

In the case of the hair cell cilia, deflection of the bundle toward the longest cilium causes the distance between the tips of successive cilia to become greater, and the connecting filaments are stretched more than at rest (see Fig. 18.4B). More of the mechanosensitive channels open, more positive charge

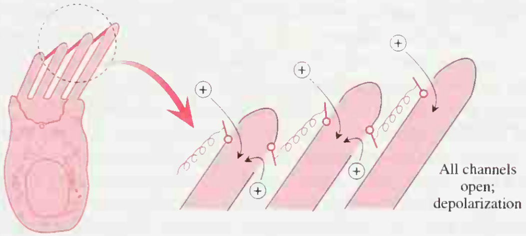
Figure 18.4

A schematic representation of the mechanotransduction process in hair cell cilia. (A) In the resting state, there is some tension on the filaments (red) connecting the tips of adjacent cilia. Some mechanosensitive cation channels are therefore open, and the hair cell is partially depolarized because of the influx of positive charge. (B) When the cilia are deflected toward the longest cilium, the distance between the filament attachment points increases, all cation channels open, and the hair cell depolarizes more strongly. (C) When the cilia are deflected away from the longest cilium, the tension exerted by the connecting filaments is lessened, all channels close, and the hair cell hyperpolarizes.

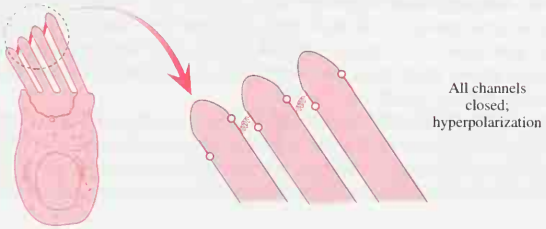
A. Resting state



B. Deflection toward longest cilium



C. Deflection away from longest cilium



enters the cell, and the hair cell depolarizes. Conversely, when the direction of deflection is away from the longest cilium, the distance between tips of adjacent cilia becomes smaller (see Fig. 18.4C). The connecting filaments are less stretched, and the reduced tension causes mechanosensitive cation channels to close. For this direction of movement, the hair cell hyperpolarizes because the cation conductance is smaller than it is in the resting state.

THE MAMMALIAN EAR

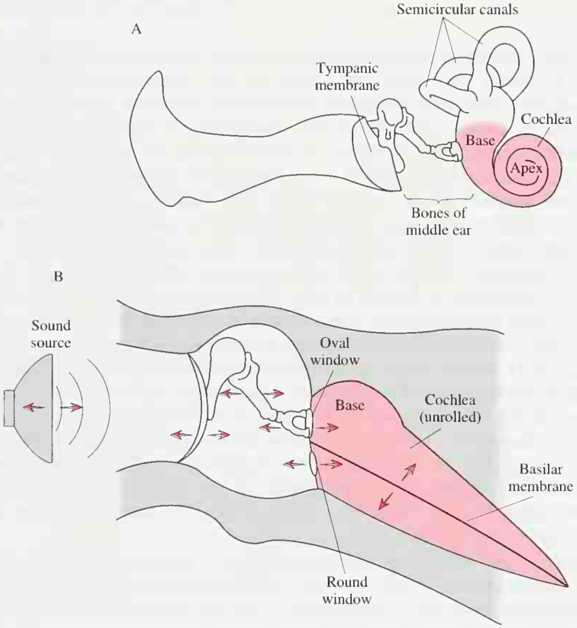
The ear is the specialized organ for sensing airborne vibrations in mammals. Figure 18.5 shows the basic structure of the mammalian ear. The mechanosensory cells that transduce mechanical vibration into electrical signals in the ear are also hair cells. In this case, however, the cells are located within a spiral-shaped bony enclosure within the inner ear, called the **cochlea.** The cochlea can be thought of as an outgrowth of the vestibular labyrinth, whose function in the perception of head motion was discussed in chapter 12. Indeed, the cochlea developed during the course of evolution as an additional chamber of the phylogenetically older vestibular apparatus.

Like the labyrinth and the even more primitive lateral line system, the hair cells of the cochlea are bathed in fluid. Vibrations in the air reaching the ear of a terrestrial mammal must be transferred to this fluid. This coupling of airborne vibrations to the fluid within the cochlea is the job of the middle ear (see Fig. 18.5). The ear drum, or **tympanic membrane,** is stretched across the ear canal like the head of a drum and separates the middle ear from the external world. Air vibrations set the ear drum in motion, and this motion is transferred to the cochlea via the small bones of the middle ear (the hammer, anvil, and stirrup). Because the walls of the cochlea are rigid, the movement of the bones is transferred to the interior of the cochlea via a flexible membrane, called the **oval window,** located at the point where the bones of the middle ear contact the cochlea.

The cochlea is divided into two compartments by another membrane, the *basilar membrane.* (As we will see later, the anatomical arrangement is actually more complicated than two compartments, but this description will suffice for understanding the mechanical coupling within the cochlea.) If a wave of increased pressure arrives at the ear drum, the oval window is pushed inward, increasing the pressure above the basilar membrane. For this increased pressure to deflect the basilar membrane, another flexible membrane is required within the cochlear compartment *below* the basilar membrane. This flexible membrane, called the **round window,** bulges outward, allowing the pressure increase in the upper compartment to move the basilar membrane downward. If a wave of decreased pressure reaches the ear drum, the oval window is pulled outward, the round window bulges inward, and the basilar membrane moves upward. Therefore, an oscillation of the tympanic membrane produces an oscillatory movement of the basilar membrane inside the cochlea (see Fig. 18.5B).

Figure 18.5

An overview of the structure of the human ear. (A) The outer ear is separated from the middle ear by the tympanic membrane, whose vibrations are transmitted to the cochlea (pink) via the bones of the inner ear. (B) The cochlea is represented here in a straightened form to clarify its internal structure. In this diagram, the separation between the upper and lower compartments of the cochlea is simplified, in that the separation is represented solely by the basilar membrane. (See Figure 18.12 for a more complete view of the internal structure of the cochlea.)



The sensory hair cells ride on top of the basilar membrane, and the hair bundles of the hair cells are deflected in response to vibrations of this membrane (as discussed later in this chapter). The cell bodies of the sensory neurons that receive synaptic inputs from the hair cells are located within the cochlea, in the **spiral ganglion.** Each spiral ganglion cell sends an axon into the central nervous system via the **auditory nerve.** Together with the axons coming from the vestibular apparatus (the vestibular nerve), these axons make up **cranial nerve VIII.**

Response of single auditory nerve fibers: tuning curves

Natural sounds consist of complex combinations of vibrations at many different frequencies. The responses of neurons in the auditory system can be understood, however, by examining a much simpler sound stimulus. If we play a sinusoidal driving voltage into a loudspeaker (Fig. 18.6A), the movements of the speaker cone will produce a sine wave sound stimulus, which will be experienced by a human listener as a pure tone whose pitch depends on the frequency of the sine wave. We can also vary the intensity of the stimulus and determine the listener's sensitivity to stimuli of different frequencies. Normal human listeners can detect sounds in the frequency range from 20 cycles/s (Hz) to approximately 20,000 Hz, with the greatest sensitivity being in the range of 1000 to 4000 Hz.

The same type of experiment can be performed while recording the action potential activity of a single auditory nerve fiber. Each nerve fiber will be most sensitive to a specific frequency, and it will respond less well to stimuli of both higher and lower frequencies. The relationship between the sensitivity of the nerve fiber and the frequency of the stimulus defines the **tuning curve** for the fiber; examples of tuning curves are shown in Figure 18.6B. The tuning curve for an individual auditory nerve fiber is much sharper than the overall curve measured for the organism as a whole. For example, the fiber labeled A in Figure 18.6B (dashed curve) does not respond well to stimuli below 100 Hz or above 2000 Hz, although a human listener can readily detect such tones. Different auditory nerve fibers are most sensitive to different portions of the audible frequency spectrum. The fiber labeled B, for instance, responds to tones in the range of 1000 to 10,000 Hz, and is most sensitive at 5000 Hz. The patterns of action potentials triggered in fibers A and B by brief tone bursts at 500 Hz and 5000 Hz are shown in Figure 18.6C.

Figure 18.6

Tuning curves of single auditory nerve fibers. (A) A loudspeaker can be made to produce a pure tone stimulus, whose sinusoidal frequency and amplitude can be independently controlled.

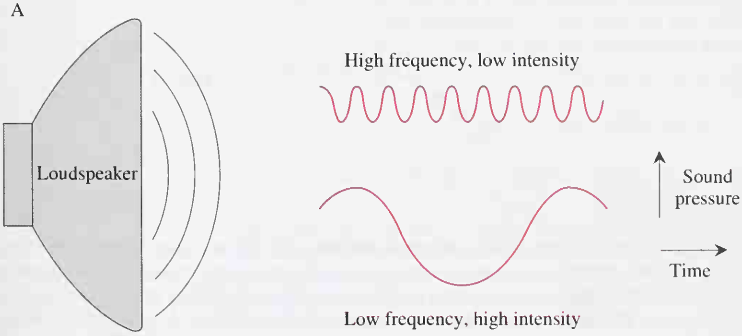
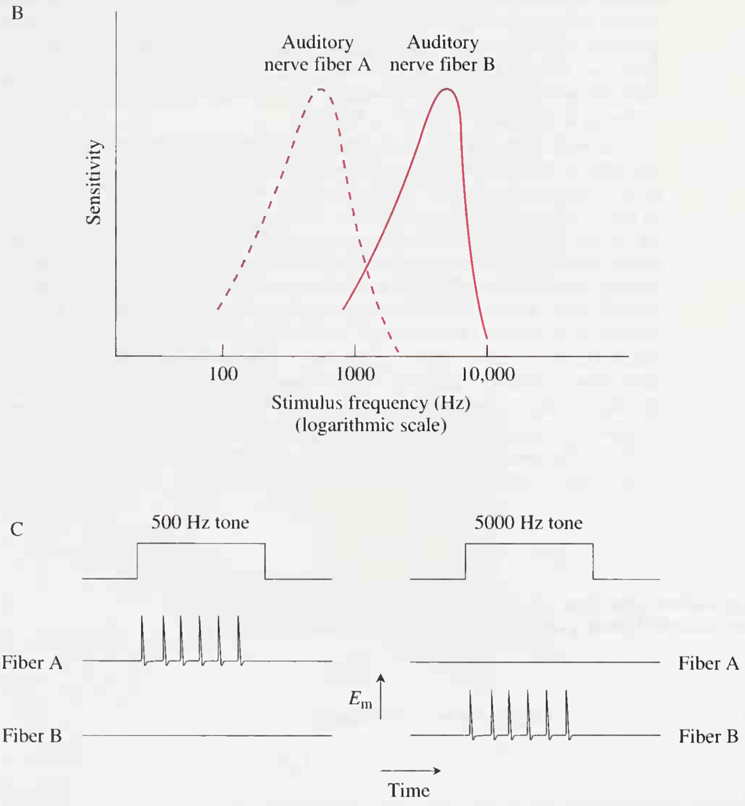


Figure 18.6 (continued)
(B) The sensitivity of two auditory nerve fibers to sinusoidal stimuli of different frequencies. High sensitivity means that the nerve fiber responds to very quiet tones; low sensitivity means that loud tones are required to elicit a response. The frequency of the sine wave stimulus is shown on a logarithmic scale. (C) Examples of action potential activity elicited in the two fibers of B by stimuli at 500 Hz (left) and 5000 Hz (right).



In humans, there are approximately 25,000 auditory nerve fibers from each cochlea. As a group, this population defines the entire audible spectrum that humans can perceive. In other species, the auditory system can respond to stimulus frequencies that humans find inaudible. A "silent," ultrasonic dog whistle is certainly not silent to your dog, for example. Bats use even higher-frequency sounds as the basis for their echolocation system.

Cochlear mechanics contribute to frequency tuning in the auditory system

Multiple mechanisms underlie the narrow frequency tuning observed for the individual auditory nerve fibers. The first mechanism we will consider is mechanical and is based on the construction of the basilar membrane. Recall that vibrations of the tympanic membrane are translated into pressure fluctuations within the fluid-filled compartments of the cochlea, producing vertical movements of the basilar membrane (see Fig. 18.5). The basilar membrane is not uniform from the base to the apex of the cochlea, however. This is illustrated in Figure 18.7. When viewed from above, the basilar membrane is tapered, with the width being smallest at the basal end and largest at the apex. Like the strings of a harp or a piano, the short end of the membrane vibrates best at high frequencies, and the long end vibrates best at lower frequencies. In addition to being narrower, the basal end of the basilar membrane is stiffer than the apical end. As a result, low-frequency sound stimuli tend to preferentially vibrate the apical end of the basilar membrane, while high-frequency sounds preferentially vibrate the basal end.

When a sinusoidal sound stimulus is received at the ear, the greatest up–down movement of the basilar membrane occurs at a particular location along the length of the cochlea, depending on the frequency of the stimulus (see Fig. 18.7). This process accounts for part of the frequency tuning of the auditory nerve fibers. Spiral ganglion neurons that receive inputs from hair cells at the apex of the cochlea will be best stimulated by low-frequency stimuli, while those that receive inputs from basal hair cells will be best stimulated by high-frequency stimuli. The frequency tuning that would be expected from the mechanical properties of the cochlea is rather broad, however, compared with the sharp tuning curves actually observed in single auditory nerve fibers (see Fig. 18.6B). As shown in Figure 18.7, the amplitude envelope for low- and middle-frequency stimuli includes most of the basilar membrane. Consequently, a broad range of stimulus frequencies would excite the nerve fibers connected to hair cells at the middle of the basilar membrane. Therefore, additional tuning mechanisms are required to explain the behavior of the auditory nerve fibers.

Hair cell electrical properties also contribute to frequency tuning

As noted earlier, hair cells respond to oscillatory movements of their hair bundles with an oscillatory change in membrane potential (see Fig. 18.3). Responses of individual hair cells, however, differ for hair-bundle movements occurring at different frequencies. Some hair cells give larger responses to low-frequency stimuli, while others produce larger responses to high-frequency stimuli. Figure 18.8 illustrates this behavior. When the hair bundle is moved back and forth slowly, a low-frequency cell follows the stimulus with

Figure 18.7
The basilar membrane vibrates most strongly at different locations in response to tones of different frequencies. The cochlea is shown in coiled and uncoiled representations at the top. When viewed from above, the uncoiled basilar membrane is wider at the apex (low-frequency end) than at the high-frequency end (base). In the side views, the red dashed lines show the maximal up–down extent of the vibrations of the basilar membrane produced by three different stimulus frequencies. The black dashed line indicates the resting, unstimulated position of the basilar membrane.

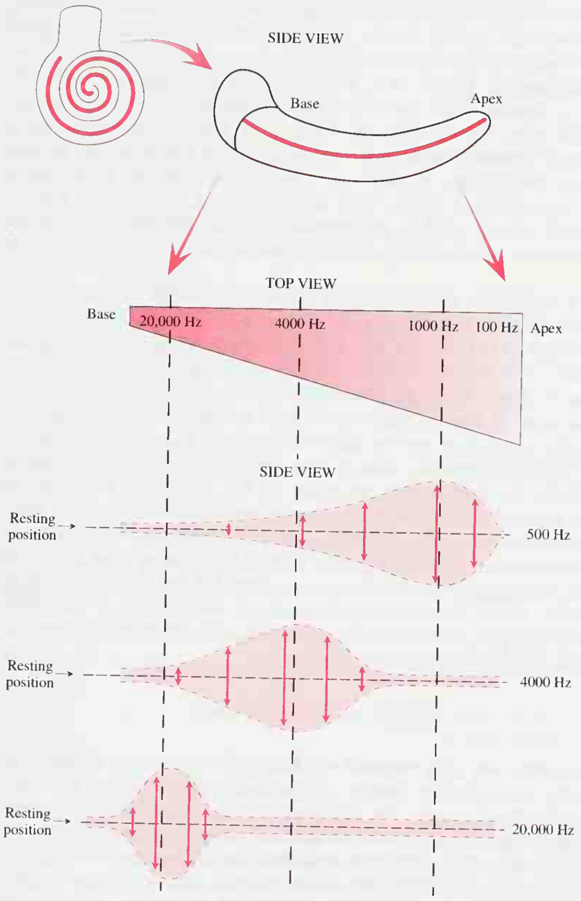
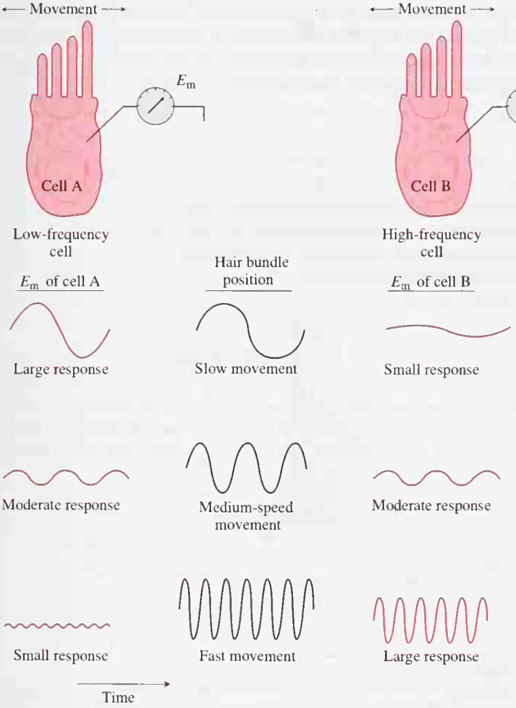


Figure 18.8
Frequency tuning in single hair cells. Hair cells have a preferred frequency of stimulation that matches the maximal vibration frequency of their location on the basilar membrane. The left column shows responses of a hair cell from a low-frequency position along the basilar membrane (toward the apex). The right column shows the responses of a hair cell from a high-frequency position (toward the base). The middle column shows the oscillatory motion applied to the hair bundles in each case.

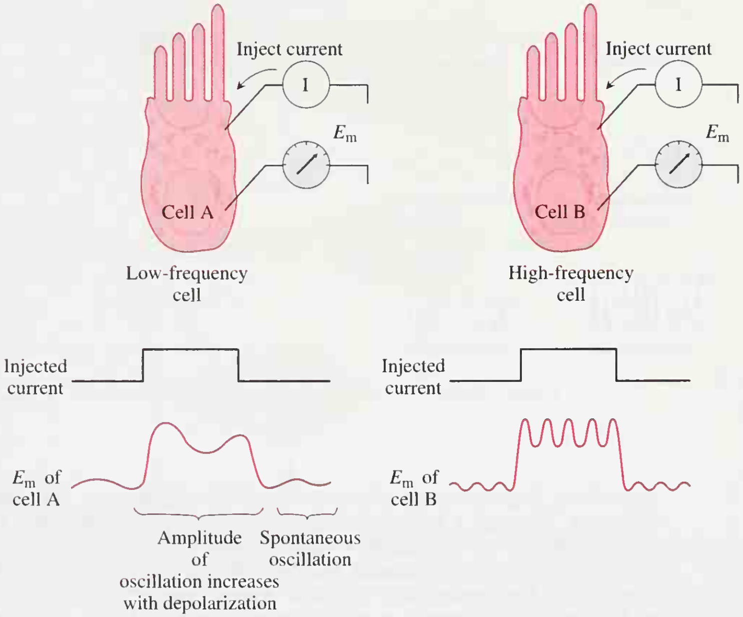


a matching, large-amplitude change in membrane potential at the same frequency. Although a high-frequency cell responds to the same sort of stimulus, the response amplitude is much smaller. When the hair bundle is moved rapidly, both cells respond, but the high-frequency cell has a large response and the low-frequency cell shows a small response. Both cells give an intermediate response to a moderate-speed movement. This variation demonstrates that individual hair cells have a characteristic frequency and respond best to a particular preferred frequency of stimulation.

The characteristic tuning frequency of an individual hair cell can also be revealed by the cell's response to electrical stimulation (Fig. 18.9). Even in the absence of a mechanical stimulus, the resting potential of an isolated hair cell often demonstrates a small oscillation at a frequency that matches the cell's characteristic frequency. In cells that respond best to low-frequency mechanical stimulation, this spontaneous oscillation of membrane potential occurs at a low frequency. In high-frequency cells, the spontaneous oscillation takes place at a high frequency. When a positive current is injected into the cell, the cell depolarizes, and the amplitude of the oscillation increases. In both high- and low-frequency cells, the speed of the oscillation matches the frequency preference of the cell for mechanical stimuli.

Figure 18.9

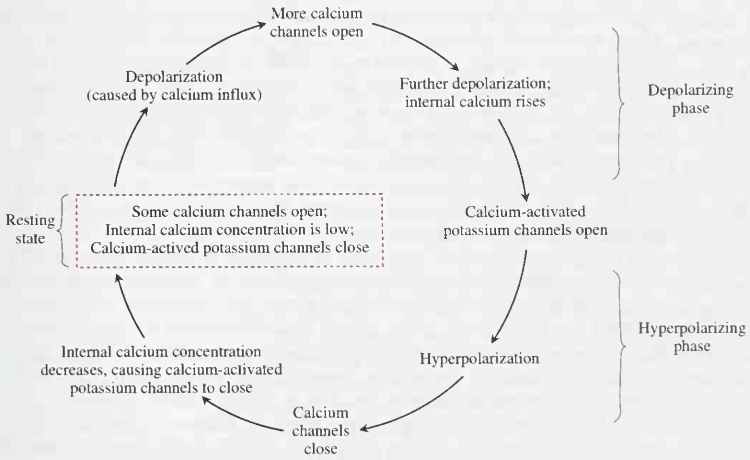
Hair cells have endogenous electrical tuning. Even in the absence of an applied stimulus, the membrane potential of hair cells oscillates. The frequency of the oscillation matches the preferred mechanical stimulation frequency of the cell. A low-frequency hair cell undergoes slow oscillations (left), while a high-frequency hair cell experiences fast oscillations (right).



These oscillations apparently result from the interplay of two different types of ion channel in the plasma membrane of the hair cell: voltage-activated calcium channels and calcium-activated potassium channels. We encountered both types of ion channels in our earlier discussion of ionic permeability mechanisms of neurons. Figure 18.10 summarizes how these channels interact to produce cyclical depolarization and hyperpolarization. In its resting state (dashed box on the left of Figure 18.10), the hair cell is depolarized slightly, and some voltage-activated calcium channels are open. The resulting influx of calcium ions tends to further depolarize the cell, opening even more calcium channels. As more calcium ions enter through the open channels, however, the internal calcium concentration rises and the calcium-activated potassium channels subsequently open. These channels oppose further depolarization and cause the membrane potential to become more negative. Hyperpolarization causes the voltage-activated calcium channels to close, which in turn decreases calcium influx. As the internal calcium concentration falls again—because of calcium pumps and cellular uptake mechanisms—the calcium-activated potassium channels close, and we return to the beginning of the cycle. In this way, repetitive cycles of depolarization and hyperpolarization are produced (see the cyclic diagram in Figure 18.10).

The depolarizing phase of the oscillations represents the opening of voltage-activated calcium channels, and the hyperpolarizing phase represents

Figure 18.10
The proposed mechanism for endogenous electrical tuning of hair cells. The resting state is indicated by the red dashed line. The depolarizing phase is represented in the upper part of the cycle, while the hyperpolarizing phase is represented in the lower part.


More calcium channels open
Further depolarization; internal calcium rises
Depolarizing phase
Depolarization (caused by calcium influx)
Resting state
Some calcium channels open; Internal calcium concentration is low; Calcium-actived potassium channels close
Calcium-activated potassium channels open
Hyperpolarizing phase
Hyperpolarization
Internal calcium concentration decreases, causing calcium-activated potassium channels to close
Calcium channels close

the opening of calcium-activated potassium channels. The frequency of the oscillation depends on the time delay between the opening of each type of channel. This delay time is short in cells that have a high characteristic frequency and long in cells that have a low characteristic frequency. The exact mechanism that determines the length of the delay remains unclear. One possibility is that the delay depends on the distance between the calcium channels and the potassium channels. If the distance is large, it takes longer for the calcium entering through the calcium channels to reach the potassium channels and to accumulate the concentration necessary to open the potassium channels.

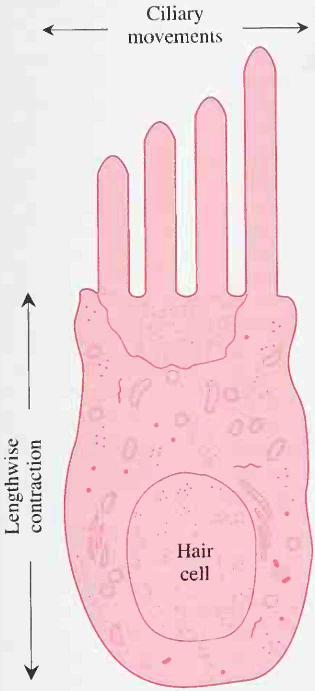
In summary, the frequency tuning of an individual hair cell reflects the characteristics of the ion channels in the cell's membrane. Thus, an electrical mechanism underlies the tuning process. The hair cells at a particular location along the basilar membrane are thought to have a preferred frequency that matches the frequency tuning of the cochlea at that position. In this way, the broad mechanical tuning of the basilar membrane is sharpened by the electrical response of the hair cells. If a 4000 Hz stimulus is presented, for example, the hair cells at the 4000 Hz position on the basilar membrane (see Fig. 18.7) will be stimulated more than the hair cells at other positions: the motion of the membrane is largest at that location, and this stimulus frequency produces the largest electrical response in the hair cells at that position. Although the basilar membrane at other positions undergoes substantial motion during the 4000 Hz stimulus (see Fig. 18.7), the frequency of the vibration does not match the preferred frequency of the hair cells at other positions, and so their response is smaller.

Hair cells also produce active movements

So far, we have been discussing the electrical responses produced by hair cells when an external stimulus sets the bundle of cilia into motion. Hair cells have also been shown to *produce* movements in response to electrical stimulation. Thus, these cells can generate active movements as well as respond passively to imposed movements. This ability should not be surprising, because cilia are commonly used to produce movement in a variety of different cell types. For instance, many single-celled organisms use ciliary motions to locomote. In the air passages of vertebrate lungs, moving cilia of epithelial cells are used to clear out debris that enters from the outside world during breathing.

Hair cells can produce two types of motions, as shown in Figure 18.11. First, the ciliary bundle moves back and forth in response to oscillations of membrane potential. The molecular motor that drives this ciliary motion is based on the protein actin, which we encountered in our description of skeletal muscle contraction mechanisms (see chapter 9). Because the oscillatory change in membrane potential has a particular characteristic frequency for a particular hair cell, the oscillatory ciliary movements produced by a given cell also have a characteristic frequency. Second, the hair cell contracts along its length. When the cell is depolarized, it contracts

Figure 18.11
Hair cells move in response to changes in membrane potential. Both the position of the ciliary bundle and the length of the hair cell change when the membrane potential is altered.



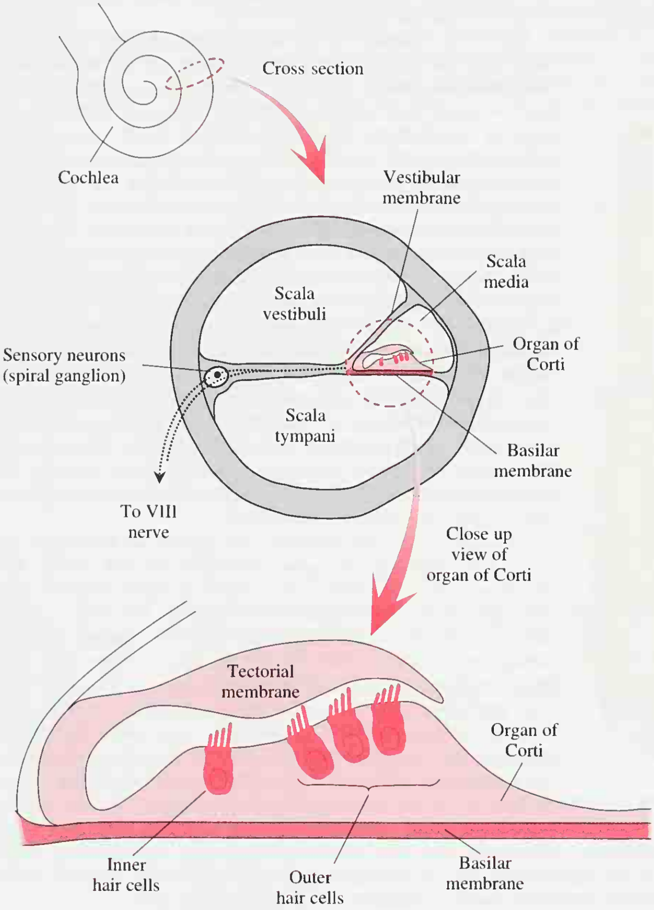
(that is, becomes shorter). Hyperpolarization causes the cell to become longer. The molecular mechanisms for this longitudinal contractile response are not yet completely established, but the motion appears to depend on a lattice of filaments located just under the plasma membrane.

The active movements of hair cells are thought to play an important role in amplifying small motions of the basilar membrane. Before examining how this mechanical amplification occurs, we must first describe additional structural details of the auditory organ within the cochlea. Figure 18.12 shows a cross section through the cochlea to reveal its organization into separate compartments. As we described earlier (see Fig. 18.5), the cochlea contains two large, fluid-filled compartments. The compartment connected to the oval window, where the incoming vibrations arrive, is called the **scala vestibuli;** the compartment connected to the round window is called the **scala tympani.** In Figure 18.12, note that these two compartments are separated by a third, smaller compartment that is bounded on one side by the basilar membrane and on the other side by the **vestibular membrane.** (The scala vestibuli and vestibular membrane are unrelated to the vestibular apparatus in the other part of the inner ear, which we discussed in chapter 12.) The third compartment is called the **scala media** (or the **cochlear duct**). The hair cells themselves are part of the **organ of Corti,** which rests on the basilar membrane and moves up and down when the membrane vibrates during acoustic stimulation.

The organ of Corti contains two groups of hair cells: the **inner hair cells** and the **outer hair cells** (see Fig. 18.12). The two types differ in several ways. There are three rows of outer hair cells along the length of the cochlea, but only a single row of inner hair cells. The entire cochlea contains approximately five times as many outer hair cells as inner hair cells (about 20,000 versus about 4000). In addition, the outer hair cells are larger than the inner hair cells and have larger hair bundles. Unlike the cilia of the inner hair cells, the cilia of the outer hair cells are imbedded in an overlying membrane, the **tectorial membrane.** When the basilar membrane moves up and down, the shearing motion generated between the tectorial membrane and the underlying hair cells deflects the hair bundles of the outer hair cells. The inner hair cells, on the other hand, are coupled to the relative movements of the basilar and tectorial membranes indirectly via the motions of the intervening fluid.

These differences would seem to suggest that the outer hair cells are likely to play a more important role than the inner hair cells in auditory transduction. A surprise awaits us, however, when we examine the pattern of innervation of the inner and outer hair cells by the sensory neurons of the spiral ganglion. Almost all of the sensory neurons make synaptic contact exclusively with inner hair cells: for every sensory neuron that contacts outer hair

Figure 18.12
The internal structure of the cochlea viewed in cross section.



cells, approximately 20 contact inner hair cells. Thus, the great majority of auditory nerve fibers reflect the responses of the inner hair cells. Because the outer hair cells are much more numerous, each of the few sensory axons that innervate the outer cells must contact a large number of cells (approximately 20). The opposite situation occurs for the inner hair cells, where innervating nerve fibers outnumber hair cells. Thus, each inner hair cell synapses onto several sensory neurons (5–10 per hair cell). So the inner hair cells, not the more numerous outer hair cells, are largely responsible for generating the sensory signal in the cochlea.

The primary function of the outer hair cells may be to mechanically amplify tectorial membrane motion. The outer hair cells move in response to depolarization and hyperpolarization, as described earlier (see Fig. 18.11). By adding a component of active motion, the cilia of the outer hair cells attached to the tectorial membrane reinforce vibrations at the preferred frequency. This hypothesis explains why there are so many outer hair cells and why their ciliary bundles are larger than those of inner hair cells. The longitudinal contractions of the hair cells (see Fig. 18.11) are also important in amplifying small motions of the basilar membrane. Because the outer hair cells are attached to the tectorial membrane via their cilia and are imbedded in the organ of Corti, they pull up on the basilar membrane when they contract. Similarly, when the outer hair cells elongate during hyperpolarization, they push down on the basilar membrane. The electrical tuning of the outer hair cells guarantees that these motions occur at the preferred frequency of each cell, which matches the preferred frequency of the basilar membrane at each position along the cochlea. Thus, the outer hair cells mechanically increase the size of basilar membrane vibrations imposed by an auditory stimulus and do so preferentially at the location that is best stimulated by the stimulus.

Efferent synapses onto hair cells

The nerve fibers of the spiral ganglion neurons receive excitatory synapses from the hair cells and carry the outgoing, or afferent, sensory information into the brain. There are also incoming nerve fibers in the cochlea that originate from neurons in the brainstem. These efferent nerve fibers make synapses onto the hair cells (predominantly outer hair cells). Activation of the efferent neurons reduces the sensitivity of the cochlea to sound and inhibits the sensory output from the ear. Thus, the efferent synaptic connections produce negative feedback on the auditory transduction system.

The neurotransmitter released by the efferent synaptic terminals is acetylcholine, which acts via muscarinic cholinergic receptors to open potassium channels in the hair cells. The increase in potassium permeability hyperpolarizes the outer hair cells, inhibits the oscillations of membrane potential, and inhibits the motor movements of the cilia. The fact that the outer hair cells are the principal target of the efferent input provides further evidence for the importance of the outer cells in regulating the sensitivity of the cochlear transduction mechanisms.

THE AUDITORY SYSTEM IN THE BRAIN

Cochlear nucleus

After the auditory nerve enters the central nervous system, the distribution and processing of auditory information follows a pattern similar to that of other sensory systems. The first stop is the *cochlear nucleus* in the brainstem, where the auditory nerve fibers terminate. The auditory nerve fibers originating from different parts of the cochlea are geometrically mapped onto specific regions within the cochlear nucleus. Recall that each position along the cochlea is most sensitive to a particular stimulus frequency. The spatial mapping of the cochlea onto the cochlear nucleus means that the cochlear nucleus also has a map of preferred stimulus frequency. This **tonotopic map** is analogous to the retinotopic map found within the visual system.

The tonotopic map is important because the auditory nervous system can determine the stimulus frequency only by identifying which part of the cochlea is activated. If the sound stimulus occurs at a frequency of a few hundred hertz or lower, the auditory nerve fibers are able to produce bursts of action potentials that track the frequency of the stimulus (see Fig. 18.3). At frequencies above a few hundred hertz (which include most of the audible frequency spectrum for humans), however, the auditory nerve fibers can no longer follow the cycle-by-cycle pressure variations of the stimulus. In this case, the temporal pattern of the action potentials cannot carry information about the frequency of the stimulus itself. Thus, each auditory nerve fiber can be thought of as a labeled line that signifies the presence of a particular auditory stimulus frequency. Only by keeping precise track of the labels on the lines—via the tonotopic spatial organization in the cochlear nucleus—can the nervous system analyze the overall frequency content of the stimulus.

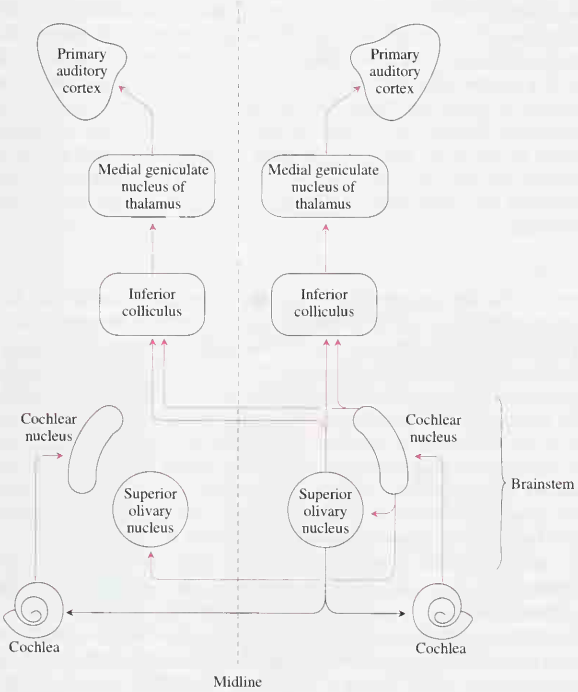
The neurons in the cochlear nucleus respond to other specific aspects of the auditory stimulus in addition to the stimulus frequency. Some cochlear nucleus neurons fire only a single action potential abruptly and reliably just at the onset of a tone at their preferred frequency. These neurons extract precise information about the time of onset of an arriving sound stimulus. Other neurons in the cochlear nucleus show the opposite pattern of response, remaining silent at the onset of a stimulus and then increasing their firing rate during a sustained tone. These cells transmit information about the ongoing intensity of a sound. Although several other variants of these response patterns exist, the important point is that the inputs from the cochlea are analyzed in the cochlear nucleus to extract particular kinds of information about the auditory stimulus. These information signals are then transmitted to other portions of the auditory system in the brain for further analysis and processing, in a pattern similar to that followed with information processing in the visual system (see chapters 16 and 17).

Superior olivary nucleus

The outputs of the cochlear nucleus illustrate one of the general principles of neural organization: both hierarchical and parallel organization are observed in the anatomical connections made by the neurons of the cochlear nucleus. Figure 18.13 shows a schematic diagram of the overall pathway in the mammalian brain leading to the primary auditory cortex. The target for auditory information ascending from the brainstem is the **inferior colliculus.** Two parallel pathways lead from the cochlear nucleus to the inferior colliculus: a direct, bilateral projection of axons of cochlear nucleus neurons, and an indirect, hierarchical path via an intermediate brainstem nucleus, the **superior olivary nucleus** (also called the **superior olive**).

Neurons within the olivary nucleus serve as the source of the efferent axons that project back to the cochlea, where they make synapses on the

Figure 18.13
The schematic organization of the brain auditory pathways. Ascending paths appear in red, and feedback paths are shown in black. In the brainstem, only the connections for the nuclei on the right side are shown (to make the pattern of connections easier to follow). Mirror-image connections exist for all nuclei on the left side.



outer hair cells and control cochlear sensitivity. The main function of neurons within the superior olivary nucleus, however, is to process aspects of auditory information related to the localization of sound sources in the external environment. Clues about the location of a source relative to the head can be ascertained in two ways.

First, if a sound source is located to the left of the head, for example, the sound waves will reach the left ear sooner than the right ear. Although this time difference is very small (a few hundred microseconds), it is nevertheless detectable by specialized neurons within a subdivision of the superior olivary nucleus. These neurons receive inputs from the cochlear nuclei on both sides of the brain (**binaural inputs**) and fire action potentials only when a slight difference separates the time of activation for the inputs originating from the two ears.

Second, sounds can be localized by the small difference in the intensity of the sound in the two ears. A sound source to the left of the head will have a slightly higher intensity in the left ear than in the right ear because of the "shadowing" effect of the head. Once again, specialized neurons within a different subdivision of the superior olivary nucleus carry out a sensitive comparison of the sound intensities reported by the two ears.

Because of the subtlety of the cues involved, sound localization is not very precise in humans and in most other mammalian species. Humans (and other animals) often turn our heads from side to side as we attempt to locate the source of a sound, allowing our superior olive neurons and subsequent auditory nuclei to search for slight changes in arrival time and intensity as the head position changes. Moveable external ears offer a major advantage in this regard. In addition, animals that have a highly developed ability to localize sounds—such as bats, owls, and coyotes—often have elaborate external ear structures that maximize the intensity and arrival-time cues to improve performance.

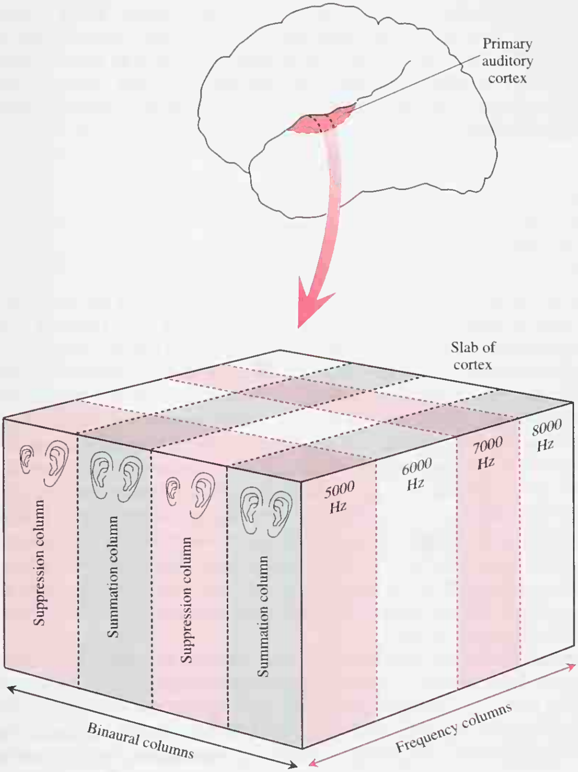
The pathway to the primary auditory cortex

The neurons of the superior olivary nucleus send projecting axons that join with the axons of cochlear nucleus neurons and ascend in a fiber tract called the **lateral lemniscus**. These axons terminate and make synaptic connections in the inferior colliculus. The outputs from both the cochlear nucleus and the superior olivary nucleus project bilaterally (see Fig. 18.13), so that the inferior colliculus on each side of the brain receives information from both ears (as do both of the superior olivary nuclei). Unlike the superior colliculus, which plays an important role in integrating sensory and motor information in the oculomotor system (see chapter 12) and thus has both sensory and motor functions, the inferior colliculus serves solely as a sensory relay station for auditory information ascending from the brainstem.

As with the other sensory systems we have studied, the gateway to the cortical regions concerned with audition goes through the thalamus. In this case, the relevant thalamic nucleus is the **medial geniculate nucleus** (see Fig. 18.13). The projections from the inferior colliculus to the thalamus, and from the thalamus to the cortex, are primarily ipsilateral. Because the inputs from the two ears are thoroughly mixed at the lower levels, the neurons in the thalamus and cortex receive binaural inputs. The primary auditory cortex is located in the superior part of the temporal lobe of the cerebral cortex (Brodmann's areas 41 and 42), as shown in Figure 18.14. The tonotopic map of the cochlea, which was first noted in the cochlear nucleus in the brainstem, is also found in the auditory cortex. As in the primary visual cortex, where the retinotopic map is repeated several times in subdivisions of the cortex specialized for different visual functions (see chapter 17), the tonotopic map in the primary auditory cortex is represented multiple times.

There are additional structural similarities between the auditory and visual cortices. In both cases, the cortex is organized into a two-dimensional array of vertically oriented columns across the cortical surface. In the visual

Figure 18.14
The location and organization of the primary auditory cortex.



cortex, these columns are the orientation columns and the ocular dominance columns (see chapter 17). In the auditory cortex, there are **frequency columns**, within which cells have the same frequency preference for sound stimuli (see Fig. 18.14). The frequency columns form one axis of the two-dimensional array. Neighboring columns have similar frequency preference, which varies in a consistent way from low frequency to high frequency across the surface of the cortex. Thus, the frequency columns are analogous to the orientation columns of the visual cortex.

The other axis of the two-dimensional array consists of **binaural columns**, which are somewhat analogous to the ocular dominance columns encountered in the visual cortex. There are two types of binaural columns, which alternate along the surface of the primary auditory cortex. All cells in the two types of alternating binaural columns receive inputs from both ears. In one type of column (called a **summation column**), the greatest response is produced when the sound stimulus is presented simultaneously to both ears. In the other type of column (called a **suppression column**), cells respond best to a stimulus in only one ear, with the response being smaller when the stimulus is presented binaurally. The functional significance of these columns is not as well worked out in auditory cortex as it is in visual cortex. Nevertheless, the columnar organization of cortical neurons into functionally related, vertically oriented units appears likely to be a common feature of the cerebral cortex.

SUMMARY

Vibrations of the air or water in which animals live are sensed by specialized hair cells, which have a bundle of modified cilia at one end. The hair cells translate movements of this ciliary bundle into electrical signals, in a process called mechanotransduction. The cilia are tethered to one another via filamentous threads near their tips. When the bundle is deflected toward the longest cilium in the bundle, these filaments exert tension on cation channels in the cilia, causing the ion channels to open. Deflection in the opposite direction (away from the longest cilium) reduces tension and causes the channels to close. Because the open channels allow positively charged ions to enter the hair cell, the cell depolarizes when the bundle is moved toward the longest cilium and hyperpolarizes when the movement is in the opposite direction. If the hair bundle oscillates back and forth, the membrane potential of the hair cell oscillates in phase with the cilia. The hair cell makes an excitatory synapse onto a sensory neuron, which reports the activity of the hair cell to the nervous system.

In the mammalian ear, the hair cells that respond to sound stimuli are located within the cochlea, a spiral-shaped compartment in the inner ear. Vibrations in the air are transferred to the fluid inside the cochlea via the tympanic membrane (ear drum) and the bones of the middle ear. Inside the cochlea, these vibrations set in motion the basilar membrane, which has the hair-cell–containing organ of Corti riding on top of it. The up–down motions of the basilar membrane stimulate the ciliary bundles of the hair cells, which make excitatory synapses on the sensory neurons of the spiral ganglion. The axons of these neurons make up the auditory nerve and carry auditory information into the brain.

Each auditory nerve fiber is sensitive to sound stimuli only within a specific frequency range. The frequency to which the fiber responds depends on the part of the cochlea innervated by the nerve fiber. Low-frequency sounds are sensed at the apical end of the cochlea, while high-frequency sounds are sensed at the basal end. The frequency tuning of the cochlea is determined by the mechanical properties of the basilar membrane, the electrical tuning of individual hair cells, and the active motions produced by hair cells in response to changes in membrane potential.

The auditory nerve fibers enter the brainstem and synapse on neurons of the cochlear nucleus. These neurons extract specific types of information about the auditory stimulus and relay their signals to the nearby superior olivary nucleus and to the inferior colliculus. The superior olivary nucleus is largely concerned with the localization of the sound source with respect to the head. Localization is determined by differences in sound arrival time and sound intensity in the two ears. From the inferior colliculus, auditory information is sent to the medial geniculate nucleus of the thalamus, which in turn relays auditory signals to the primary auditory cortex in the superior portion of the temporal lobe.

Like the primary visual cortex, the primary auditory cortex is organized into a two-dimensional array of vertical cell columns. One dimension consists of frequency columns, within which the neurons have the same preferred stimulus frequency. The other dimension consists of binaural columns, within which the cells respond best to either binaural or monaural stimulation.

19

Chemical Senses

We have previously encountered the idea of cells responding to the presence of chemical messengers in the extracellular space. This process serves as the basis of all chemical neurotransmission, in which a presynaptic cell releases a chemical substance that in turn combines with specific postsynaptic receptor sites to alter the biological state of the receiving neuron. More generally, hormonal communication within an organism is also an example of chemical signaling: the receptive cell senses the hormone and generates an appropriate biological response. In this chapter, we will generalize the concept of chemical signaling even further and examine the reception of chemical signals that originate outside the organism. As with the other senses we have considered, specialized sensory cells exist whose job it is to detect the presence of the chemical signal and generate an electrical response that can be transmitted and analyzed in the nervous system. The principal focus of this chapter will be the external chemical senses with which humans are most familiar: smell (**olfaction**) and taste (**gustation**).

DISTINCTION BETWEEN OLFACTION AND GUSTATION

The ability to respond appropriately to the chemical composition of the environment is fundamental for life and must have developed very early during evolution. Even primitive, single-celled organisms such as bacteria possess this ability. Bacteria exhibit **chemotaxis**, in which they swim toward a source of nutrients (for example, sugar or amino acids; positive chemotaxis) and away from a noxious stimulus (for example, CO_2 or high pH; negative chemotaxis). More complex single-celled animals such as *Paramecium* also demonstrate similar kinds of chemotaxic behavior. Among multicellular invertebrate animals, chemical senses are ubiquitous, and a wide variety of chemical sensory organs have evolved to provide each organism with information about its chemical environment.

We usually classify the sensory receptor organs of the chemical senses into two categories: those concerned with taste and those concerned with smell. In broad terms, the sensory modality we call gustation detects molecules associated with food, and the information provided by this sense is used to regulate ingestion. Gustation usually involves direct contact between the organism and the food material. Olfaction, on the other hand, involves the detection of molecules whose source of origin is some distance from the animal. The distinction between smell and taste is rather fuzzy, however. From the point of view of the sensory receptor cells (**chemoreceptors**), the fundamental process is identical in both cases: the detected molecule dissolves into the aqueous fluid at the cell's sensory surface and activates a specific receptor molecule on the cell's surface, thereby changing the electrical properties of the cell. This sensory transduction process is called **chemotransduction.** As we know from our own subjective experience, the sensations of taste and smell are closely related. Consider, for example, the impairment of your ability to taste food when your nose is congested from a cold.

Nevertheless, it is useful to draw a functional distinction between the sensory modalities of olfaction and gustation. In vertebrates—and particularly in mammals—the relevant sensory receptors for taste and smell are those associated with the tongue and nose, respectively. Although the sensory receptor cells in both cases are chemoreceptors, the mechanisms of sensory transduction differ in many respects. In addition, the neural pathways in the brain that process olfactory and gustatory information are quite distinct and are organized in quite different ways. For these reasons, we will treat the olfactory and taste systems separately. We will begin with a description of the chemoreceptor cells, comparing and contrasting the transduction processes in taste and olfaction. We will then move on to examine the brain mechanisms for the two systems.

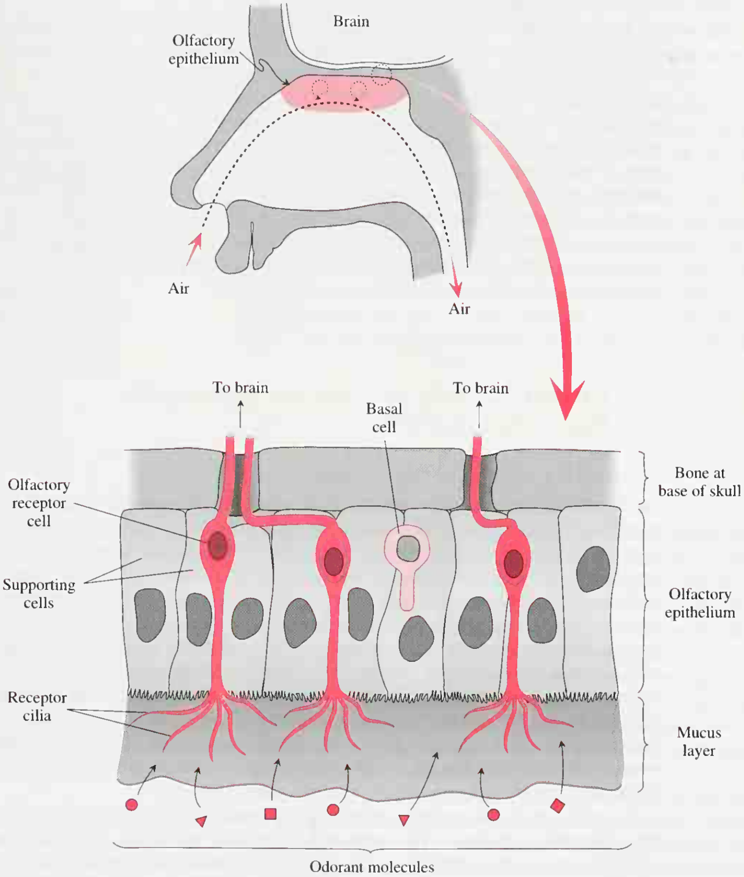
CHEMOTRANSDUCTION IN OLFACTORY RECEPTOR CELLS

Structure of the olfactory epithelium

For terrestrial animals, odors are transmitted via the air from the source to the receptive organ. Air taken in through the nose passes over the sensory surface of the olfactory apparatus before moving into the air passages that lead to the lungs. Any odorant molecules carried by the air thus have a chance to interact with the **olfactory receptor cells** (Fig. 19.1). The receptor cells are specialized neurons located within the epithelial layer lining the upper part of the nasal passage (see the lower part of Figure 19.1). The peripheral process of the olfactory receptor extends to the outer surface of the epithelial sheet, where it gives rise to several long, thin cilia. The cilia form a dense net within the layer of mucus that covers the inside of the nasal passage. The receptor molecules that interact with arriving odorants are located in the membrane of these cilia. The axons that arise from the other end of the receptor cells project directly to the brain, forming the olfactory nerve (the first cranial nerve).

In addition to the receptor neurons, two other types of cells are found in the olfactory epithelium. The **supporting cells** are epithelial cells that provide the structural backbone for the epithelium. **Basal cells** are undifferentiated neuronal precursor cells that continually give rise to new receptor cells. Unlike most other neurons, the receptor cells have a short lifespan (approximately two months) and must be replaced by newly developed ones as they degenerate.

Figure 19.1
The location and structure of the olfactory epithelium. The position of the epithelium within the nasal passage is shown in pink in the upper figure. The drawing below shows the cellular structure of the epithelial sheet. The olfactory receptor cells appear in red, the basal cells in pink, and the supporting cells in gray. The axons of the olfactory receptor cells penetrate through the bone at the base of the cranium and enter the overlying brain.



Olfactory transduction cascade

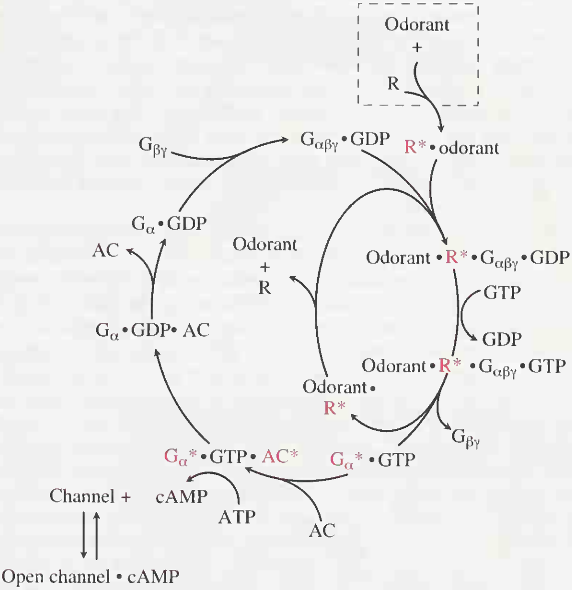
Interestingly, the transduction process in the olfactory cilia shares a number of features with phototransduction in retinal photoreceptors. In both cases, the receptor molecule that is activated by the stimulus is a member of the G-protein–coupled receptor family. In rod photoreceptors, the receptor molecule is rhodopsin. In olfaction, an odorant molecule combines with and activates an **olfactory receptor molecule,** which in turn activates a specific type of G-protein. This process is analogous to the activation of the photoreceptor G-protein, transducin, by photoactivated rhodopsin (see chapter 16). The olfactory and visual sensory transduction systems differ, however, in the number of different types of receptor molecules present in the receptor cells. The human retina contains only four types of visual pigment molecules: rhodopsin in the rods and the three cone opsins. By contrast, there are 1000 or so receptor molecules in the olfactory epithelium. This large variety reflects the fact that the odorant binding site must be specifically designed for the detection of a particular odor-producing molecule, and the system encounters many different such molecules with highly variable chemical structures.

The reactions among the olfactory receptor molecule, the odorant molecule, and the G-protein are summarized in Figure 19.2. As with other G-proteins, the activation of the olfactory G-protein involves the replacement of GDP bound to the G-protein with GTP, followed by the dissociation of the active G-protein alpha subunit from the beta and gamma subunits. In olfactory transduction, the intracellular target of the active alpha subunit is an enzyme that controls the internal concentration of a cyclic nucleotide. Although this situation is similar to that found in phototransduction, the enzyme activated by the G-protein in olfaction is a *synthetic* enzyme (adenylyl cyclase) rather than a *degradative* enzyme (phosphodiesterase). In addition, the cyclic nucleotide involved in olfactory transduction is cyclic AMP, rather than cyclic GMP. Thus, in the presence of odorant molecules, the rate of cyclic AMP synthesis increases (see Fig. 19.2). The inactivation of the activated G-protein occurs because of the endogenous GTPase activity of the alpha subunit, which is analogous to the inactivation of transducin in photoreceptors. The olfactory receptor molecule—the initiator of the cascade—deactivates upon dissociation of the odorant molecule.

Electrical response of olfactory receptor cells

The chemotransduction process alters the membrane potential of the olfactory receptor by changing the ionic permeability of the plasma membrane. The increase in cyclic AMP in the cell is coupled to the ionic permeability in the same way as in photoreceptors. Cyclic AMP directly opens cyclic nucleotide-gated cation channels in the plasma membrane of the receptor cell. These ion channels closely resemble the cyclic GMP-gated ion channels of the photoreceptor outer segment, except that they are opened by cyclic AMP rather than cyclic GMP. The cyclic AMP-gated channels are nonspecific cation channels, allowing influx of cations and thus producing depolarization of the olfactory receptor in response to odorants.

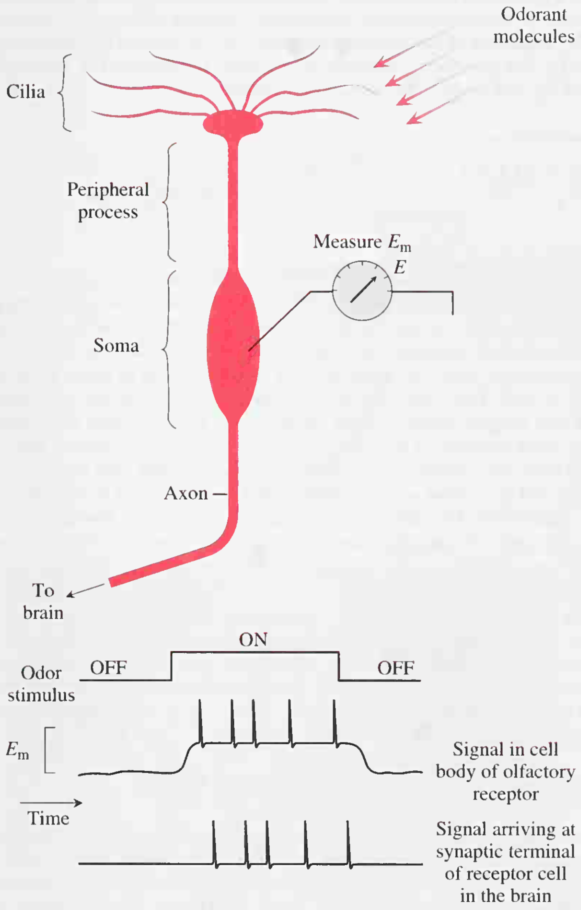
Figure 19.2
The transduction cycle for olfactory receptor cells. The entry point for the cycle is the combination of an odorant molecule with a specific receptor molecule (R) in the cilia of the olfactory receptor neuron. Activated forms of molecules are indicated in red, with an asterisk (*). (The cycle is described in detail in the text.) G_α and $G_{\beta\gamma}$ indicate the alpha and beta/gamma subunits of the olfactory G-protein, respectively. AC is adenylyl cyclase, and cAMP is cyclic AMP, which is synthesized from ATP by adenylyl cyclase.



The electrical response of an olfactory receptor neuron is illustrated in Figure 19.3. Upon receipt of an odor stimulus, the cell depolarizes because of the opening of cyclic AMP-gated cation channels in the cilia. This depolarization is the **receptor potential** of the olfactory receptor cell, and its size is graded with the intensity of the odor (that is, the number of odorant molecules that combine with receptor molecules in the cilia). Because the distance from the cilia to the soma of the receptor cell is quite short, the depolarizing receptor potential spreads to the cell body. As a result, if we record the membrane potential at the soma with an intracellular electrode (see Fig. 19.3), the electrical response to the odorant molecules can be readily detected.

The electrical response of the olfactory receptor in response to the stimulus is the opposite of the response to light in a retinal photoreceptor (see

Figure 19.3
The electrical response of an olfactory receptor neuron to an odor stimulus. The recording situation is diagrammed above, and the electrical response is shown below. When an odor stimulus is applied (top trace), both the receptor potential and the resulting action potentials are observed in the cell body of the olfactory receptor cell (middle trace). The action potentials propagate along the axon and arrive at the synaptic terminal of the receptor cell in the brain (bottom trace).


Odorant molecules
Cilia
Peripheral process
Measure E_m
E
Soma
Axon
To brain
ON
Odor stimulus
OFF
OFF
E_m
Time
Signal in cell body of olfactory receptor
Signal arriving at synaptic terminal of receptor cell in the brain

chapter 16). The photoreceptor hyperpolarizes after receiving a light stimulus because cyclic nucleotide-gated channels *close;* in the olfactory receptor, however, the stimulus causes cyclic nucleotide-gated channels to *open.*

Another difference between photoreceptors and olfactory receptors is also apparent in the electrical response shown in Figure 19.3. The depolarization produced by the odor generates action potentials, which then propagate along the axon of the receptor into the brain. Action potentials do not occur in photoreceptors, whose synaptic terminals are located near to the rest of the cell. As a result, the light-induced change in membrane potential spreads directly to the terminal without an intervening action potential. By contrast, the synaptic terminals of the olfactory receptor cells are located far away from the cell body, and so action potentials are required to transmit the electrical signal from the cell body to the synaptic terminal.

CHEMOTRANSDUCTION IN TASTE RECEPTOR CELLS

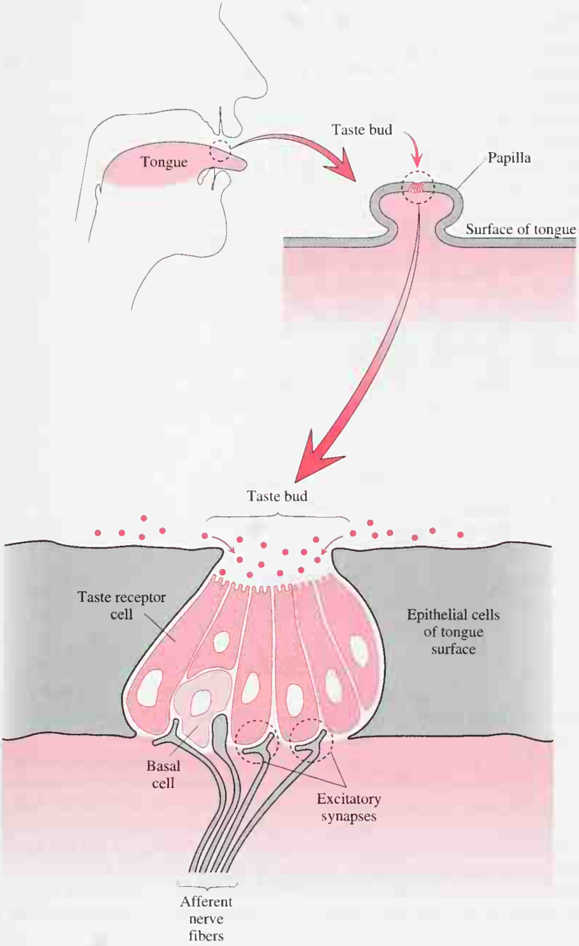
Structure of taste buds

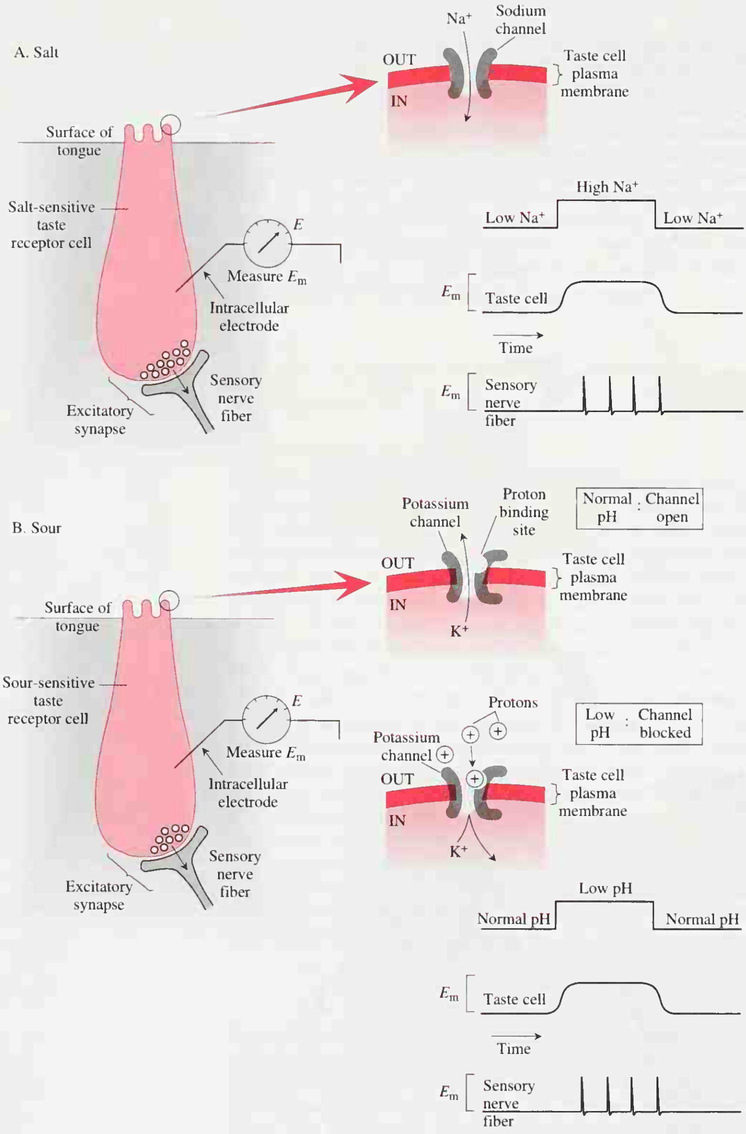
Now we will turn our attention to the chemotransduction mechanism in the other major type of chemoreceptor, the taste cells. These specialized sensory cells are found on body surfaces that come into direct contact with food. In mammals (including humans), the principal receptive surface for taste sensation is the tongue, although taste receptor cells are found in other parts of the mouth as well. The taste cells are not spread evenly over the epithelial surface of the tongue; instead, they are grouped together into structures called **taste buds** (because of their resemblance to the bud of a flower; Figure 19.4). Each taste bud contains about 100 taste receptor cells. The top surface of each taste cell is covered with microvilli, which are exposed to and detect chemicals dissolved in the saliva on the surface of the tongue. The taste buds are in turn grouped into **papillae** (see Fig. 19.4), which take the form of either protrusions or trenches on the surface of the tongue. Like the olfactory receptors, the taste receptor cells have a limited lifespan. Consequently, basal cells within the taste bud continually differentiate into new receptor cells to replace the old ones as they die off. Unlike the olfactory receptors, however, the taste receptor cells have no axons and remain entirely confined within the taste bud. Information is carried into the central nervous system from the taste buds by the axons of sensory neurons, which receive excitatory synaptic contacts from the taste receptor cells (see Fig. 19.4).

Transduction mechanisms in taste receptor cells: salt and sour tastes

Naturally occurring taste stimuli are complex combinations of various chemical substances that give rise to complex subjective experiences of food flavor. Despite this variety of experiences, there are only four underlying subgroups (or **submodalities**) of taste: **salty**, **sour**, **sweet**, and **bitter.** Combinations of these four dimensions account for human perceptions of complex tastes

Figure 19.4
The location and structure of taste buds. Taste buds are imbedded in the epithelial surface of the tongue, as shown in the upper diagram. The lower diagram shows the cellular organization of a taste bud. The taste receptor cells appear in pink, the basal cells in light pink, and the afferent nerve fibers that receive synapses from the taste cells in gray. The taste cells make excitatory synapses onto the afferent nerve fibers. Each taste cell synapses onto an afferent nerve fiber, although the figure shows only four synaptic connections for the sake of clarity.





A. Salt

B. Sour

Na^+
Sodium channel
OUT
IN
Taste cell plasma membrane
Surface of tongue
Salt-sensitive taste receptor cell
E
Measure E_m
Intracellular electrode
Sensory nerve fiber
Excitatory synapse
High Na^+
Low Na^+
Low Na^+
E_m
Taste cell
Time
E_m
Sensory nerve fiber
Potassium channel
Proton binding site
Normal pH : Channel open
OUT
IN
K^+
Taste cell plasma membrane
Surface of tongue
Sour-sensitive taste receptor cell
E
Measure E_m
Intracellular electrode
Sensory nerve fiber
Excitatory synapse
Protons
Potassium channel
Low pH : Channel blocked
OUT
IN
K^+
Taste cell plasma membrane
Low pH
Normal pH
Normal pH
E_m
Taste cell
Time
E_m
Sensory nerve fiber

(together with the contribution to flavor perception from the olfactory system, which is stimulated by aromatic compounds in foods). Salty stimuli are those with a high concentration of sodium ions. Sour taste arises from the application of acidic solutions, which contain a high concentration of protons. The natural stimulus for sweet sensations is sugars of various kinds (such as sucrose), while bitter taste is stimulated by a variety of organic compounds, including some amino acids.

Each of these submodalities of taste has a different transduction mechanism. Salty and sour stimuli do not have a true "receptor" molecule in the same sense as the olfactory receptor molecules described earlier. Instead, the ions (sodium or hydrogen ions for salt and sour, respectively) interact directly with ion channels to alter the membrane potential of the taste receptor cell. Because the sweet and bitter submodalities usually involve the detection of more complicated molecules that generally do not directly interact with ion channels, the transduction mechanisms for these tastes resemble those seen in olfactory transduction and phototransduction. Specific membrane receptor molecules bind the substances perceived as sweet or bitter, and the occupied receptor in turn activates intracellular signals that indirectly affect the ionic permeability of the taste receptor cell. Substances that are perceived as sweet have a wide variety of molecular structures, as do bitter substances. Thus, taste cells actually contain many different sweet and bitter receptor molecules, each of which has its receptor binding site sculpted to fit a particular stimulus molecule. Because the salty and sour submodalities are less complex, we will consider these transduction mechanisms first, before examining the sweet and bitter submodalities.

The simplest sensory transduction scheme is that used by salt-sensitive taste receptor cells (Fig. 19.5A). Open sodium channels are located in the plasma membrane of the taste cell at the top surface, where the membrane is exposed to the fluid covering the tongue. Under resting conditions, this fluid is ordinary saliva, which contains a low concentration of sodium ions. Thus, even though the sodium channels are open, little sodium flows into the cell through the open channel and the membrane potential remains at its normal negative resting value. If a food with a high salt content is ingested, however, the sodium content of the saliva increases, sodium ions enter the taste receptor cell, and the cell becomes depolarized. This

Figure 19.5
Chemotransduction in salt- and sour-sensitive taste receptor cells. (A) A salt stimulus depolarizes a salt-sensitive taste cell. The recording configuration is shown on the left and the electrical responses on the right. The sodium ions in the saliva enter the taste cell via sodium channels, depolarizing it. The depolarization increases the release of excitatory neurotransmitter from the taste receptor cell, and the firing rate of the sensory neuron increases. (B) A sour stimulus arises from an increase in the proton concentration of the saliva (low pH). The sour-sensitive taste cell has a particular type of potassium channel that remains open under resting conditions. Protons block this potassium channel, reducing the potassium permeability of the receptor cell and causing a depolarization. The depolarization increases the release of excitatory neurotransmitter and accelerates firing of action potentials by the sensory neuron.

depolarizing receptor potential increases the release of excitatory transmitter from the receptor cell, causing the sensory neuron that receives synaptic input from the receptor to fire a train of action potentials (see Fig. 19.5A). In addition, at least in some species, the taste receptor cell includes voltage-dependent sodium and calcium channels that add to the depolarization produced by the receptor potential, amplifying the response of the sensory cell. Thus, for a salty taste stimulus, the stimulus chemical itself is an ion whose influx into the cell directly produces the receptor potential.

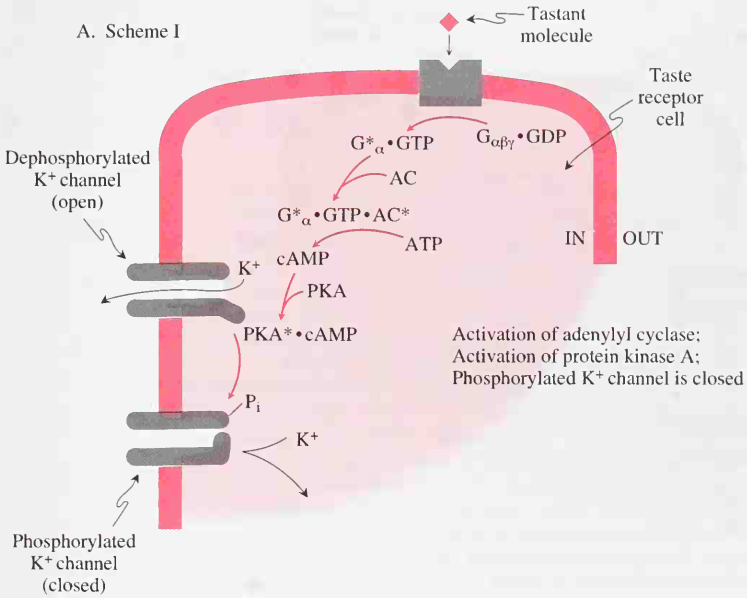
For sour taste, the transduction mechanism is only slightly more complicated. The stimulus in this case is an increase in acidity of the saliva—that is, an increase in the concentration of hydrogen ions (protons) in the fluid bathing the top surface of the receptor cell. When the proton concentration increases, the sour taste receptor cell depolarizes. Like sodium ions, hydrogen ions are cations. In this case, however, the depolarization does not result from direct permeation of protons through open cation channels (as was the case for the salt-sensitive taste cells). Instead, the protons act as channel *blockers* in the manner illustrated in Figure 19.5B. External protons block potassium channels located in the upper part of the cell, which are exposed to the saliva. When a proton occupies the proton-binding site of this type of potassium channel, potassium ions are prevented from moving through the channel pore, thereby reducing the membrane permeability to potassium. This reduction in potassium permeability produces a depolarizing receptor potential, an increase in excitatory transmitter release, and an increased rate of action potentials in the sensory neuron that contacts the receptor cell. As with the salt-sensitive receptor cells, the generator potential in some species is amplified by voltage-dependent sodium and calcium channels that respond to the depolarization induced by closure of the pH-sensitive potassium channels.

Transduction mechanisms in taste receptor cells: sweet and bitter tastes

The chemical substances that give rise to sweet and bitter sensations are detected by receptor molecules at the sensory surface of the taste cells. Although these receptor molecules have not yet been characterized, they are coupled to their intracellular actions via G-proteins. Thus, like the olfactory receptor molecules and the visual pigment molecules, the sweet and bitter receptor molecules are members of the family of G-protein–coupled receptors. As in olfactory transduction and phototransduction, cyclic nucleotides (either cyclic AMP or cyclic GMP) are the internal second messengers whose levels are controlled by the enzymes activated by the G-proteins. The cyclic nucleotides in turn regulate the open state of ion channels, thereby affecting the membrane potential of the receptor cell.

The details of the coupling among the G-proteins, cyclic nucleotides, and ion channels have not yet been completely worked out, but two possible schemes are illustrated in Figure 19.6. In scheme I, the activated taste receptor molecule turns on a particular type of G-protein that in turn activates the cyclic AMP synthetic enzyme, adenylyl cyclase—just as in olfactory transduction. Thus, a taste stimulus increases the intracellular concentration of cyclic AMP. However, the effect of the cyclic AMP on membrane ionic permeability

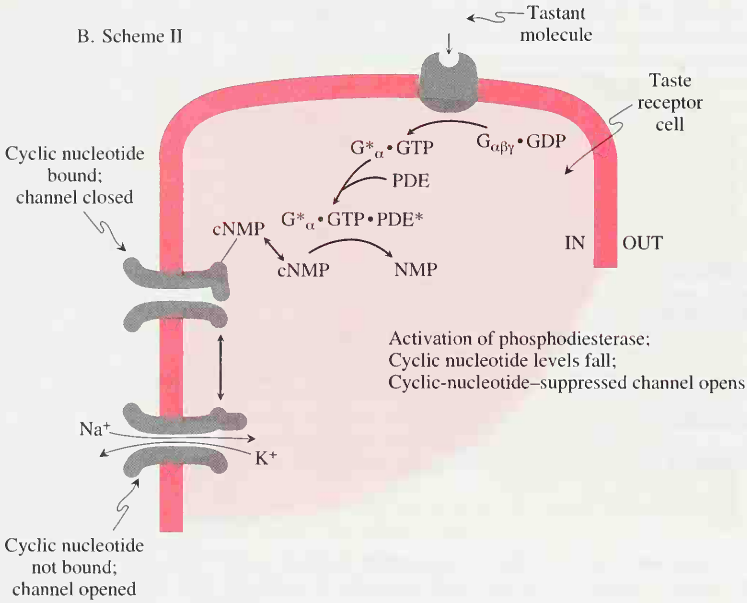
Figure 19.6
Two schemes for taste transduction using indirect coupling between the activated receptor molecule and ionic permeability of the receptor cell. (A) Scheme I: The molecules of the taste stimulus activate a G-protein–coupled receptor molecule. The G-protein increases the activity of adenylyl cyclase (AC), which in turn increases the internal concentration of cyclic AMP (cAMP). cAMP activates protein kinase A (PKA), which phosphorylates and closes potassium channels.


A. Scheme I
Tastant molecule
Taste receptor cell
$G_{\alpha\beta\gamma}$•GDP
G^*_α•GTP
AC
G^*_α•GTP•AC*
ATP
cAMP
PKA
PKA*•cAMP
P_i
K^+
K^+
IN
OUT
Dephosphorylated K^+ channel (open)
Phosphorylated K^+ channel (closed)
Activation of adenylyl cyclase;
Activation of protein kinase A;
Phosphorylated K^+ channel is closed

of the taste cell is different from its action in olfactory receptors. Instead of a direct effect on a cyclic-nucleotide–gated ion channel (as in olfaction), the cyclic AMP is thought to activate protein kinase A (cyclic AMP-dependent protein kinase), which in turn phosphorylates potassium channels. The phosphorylated potassium channels close, causing the potassium permeability of the taste receptor to decrease. This decline in potassium permeability produces a depolarizing receptor potential, which is reflected in increased action potential activity in the sensory neuron that receives synaptic input from the taste receptor cell.

Scheme II for the coupling between the activated tastant receptor and membrane permeability is shown in Figure 19.6B. Once again, the first step in the sequence is activation of an intermediary G-protein. In this scheme, however, the G-protein targets phosphodiesterase—which cleaves cyclic

Figure 19.6 (continued)
(B) Scheme II: The taste stimulus is detected by a receptor molecule that activates a G-protein, which then activates a phosphodiesterase enzyme (PDE). In response, the internal concentration of cyclic nucleotides (cNMP, including both cyclic AMP and cyclic GMP) decreases. Because the cyclic nucleotides keep nonspecific cation channels closed, the fall in cNMP concentration causes the channels to open and the cell depolarizes.


B. Scheme II
Tastant molecule
Taste receptor cell
Cyclic nucleotide bound; channel closed
$G^*_\alpha \cdot GTP$
$G_{\alpha\beta\gamma} \cdot GDP$
PDE
$G^*_\alpha \cdot GTP \cdot PDE^*$
cNMP
cNMP
NMP
IN
OUT
Activation of phosphodiesterase;
Cyclic nucleotide levels fall;
Cyclic-nucleotide–suppressed channel opens
Na^+
K^+
Cyclic nucleotide not bound; channel opened

nucleotides—rather than the synthetic enzyme, cyclase. In this regard, the proposed scheme resembles phototransduction. In fact, the type of G-protein involved is quite similar to the G-protein of phototransduction, which is called transducin (see chapter 16). To reflect this relationship, the taste-cell G-protein is called **gustducin** (for *gust*atory trans*ducin*). In this scenario, then, a taste stimulus decreases the intracellular cyclic nucleotide level. Although this action is the opposite change in cyclic nucleotide concentration from that postulated in scheme I, it has the same effect on the membrane potential: a depolarizing receptor potential. Cyclic nucleotides are thought to combine with and *close* cation channels in the membrane of the taste cell. When the cyclic nucleotide concentration falls inside the taste receptor cell in response to a taste stimulus, the cation channels open and the cell depolarizes.

The detection of sweet substances probably occurs via the G-protein pathway leading to activation of adenylyl cyclase, an increase in cAMP, and subsequent closure of potassium channels (scheme I in Figure 19.6A). Evidence also suggests that bitter taste transduction involves the other G-protein pathway, which leads to increased activity of phosphodiesterase and a decrease in cyclic nucleotide levels (scheme II in Figure 19.6B). It is not yet certain, however, that the two schemes are segregated into two different functional types of taste receptor cells.

PROCESSING OF TASTE INFORMATION IN THE BRAIN

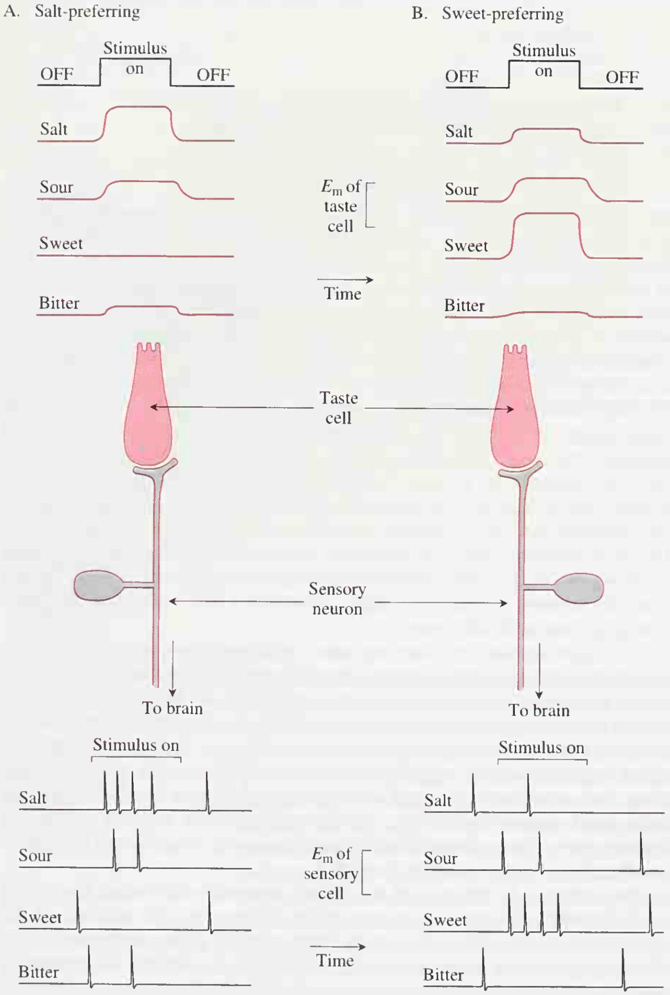
Sensory coding in the taste system

We will now turn our attention to the processing of the sensory information after it leaves the receptor cells. In the taste system, we must first consider how the submodalities (salt, sour, sweet, and bitter) are encoded at the level of the receptors and at the level of the sensory neurons to which they are connected. One simple way to separate the different types of taste stimulus would be to have a different type of taste cell specific for each of the four submodalities. This situation is not the case in reality, however. Individual taste receptor cells actually depolarize in response to more than one type of chemical stimulus, although the response for each cell is largest to one submodality. In the taste cells illustrated in Figure 19.7, for example, one cell produces the largest depolarization in response to a salt stimulus and the other in response to a sweet stimulus. The sensory neuron that receives synaptic input from the salt-preferring taste cell fires most strongly during a salt stimulus, but also is weakly excited by sour and bitter stimuli (see Fig. 19.7A). A different pattern of activation is observed with the sensory neuron receiving input from the sweet-preferring taste cell (see Fig. 19.7B). In this case, the sensory neuron is strongly excited by a sweet stimulus, but only weakly by sour and salt stimuli.

Although the taste cells demonstrate a preferential response to a particular submodality, the rate of action potentials reaching the brain in the axon of any individual sensory neuron does not provide an unambiguous indication of the kind of taste stimulus present. For example, a given rate of action potentials in the sweet-preferring neuron of Figure 19.7B could reflect a dilute sugar stimulus or a highly salty stimulus. Higher-order neurons examining the output of this single sensory cell would not be able to tell the difference between the two very different taste stimuli. Only by comparing the response patterns from different types of sensory neurons can the stimulus characteristics be uniquely discerned.

For example, in the case of the dilute sugar stimulus versus the strong salty stimulus, the nervous system could distinguish the two stimuli by comparing the activity in the two example neurons shown in Figure 19.7. If the sweet-preferring neuron fires at an elevated rate but the salt-preferring neuron does not, then the stimulus is sweet. If the salt-preferring neuron is

Figure 19.7
Encoding of sensory information in the taste system. The upper traces show the electrical responses of taste cells to stimuli of the four submodalities (salt, sour, sweet, and bitter). The lower traces show the resulting action potential activity in the sensory neurons receiving synaptic input from the taste cells. (A) Responses originating in a taste receptor cell that responds best to salty stimuli. (B) Responses originating in a sweet-preferring taste receptor cell. In each case, the taste cell and the sensory neuron respond to more than one submodality.



more strongly excited than the sweet-preferring neuron, then the stimulus is salty.

This situation is analogous to the detection of color in the visual system, where the outputs from the three types of cone photoreceptors are compared at higher levels in the visual system to distinguish the color of a visual stimulus. In the visual system, however, the comparison is carried out among receptor signals along a single *physical dimension* of the stimulus (wavelength of light); in the taste system, the comparison involves four different *categories* of chemicals (the four submodalities). Thus, the perception of a taste stimulus is governed by the representation of the stimulus on four internally generated, subjective dimensions, while the perception of color is based in large measure on a physical aspect of the stimulus itself.

Anatomical organization of the taste sensory pathway

The axons of the sensory neurons that innervate the taste buds are found in **cranial nerve VII** (the **facial nerve**) and **cranial nerve IX** (the **glossopharyngeal nerve**). The facial nerve carries the inputs from the anterior part of the tongue, and the glossopharyngeal nerve carries the inputs from the posterior part. In addition, these two nerves contain the sensory fibers of the somatosensory receptors of the tongue (touch, pressure, and temperature). The tongue sensory fibers enter the central nervous system in the medulla and make synaptic connections in the nucleus of the solitary tract (Fig. 19.8). We encountered this relay nucleus earlier, in our discussion of the autonomic nervous system (see chapter 13). The neurons in the nucleus of the solitary tract also receive sensory inputs from a variety of body organs involved in homeostatic functions, including the gut, the lungs, and the cardiovascular system. As the projection of the taste sensory fibers to this same medullary nucleus indicates, one function of taste sensory information is to contribute to the regulation of feeding behavior and the control of the viscera in the evolutionarily ancient part of the brain. Indeed, in organisms that lack a well-developed forebrain, taste sensory information has no other function. In the nucleus of the solitary tract, the inputs from the taste buds are segregated from the somatosensory tongue inputs and make connections in a specific subdivision called the **gustatory nucleus**.

The neurons of the solitary nucleus that receive inputs from the tongue send their ascending axons to two principal targets, which differ in importance in different species, depending on the role played by the thalamocortical pathway in sensory information processing. The first, evolutionarily older target is the **pontine taste nucleus** in the dorsal part of the pons. This nucleus transmits taste sensory information to the hypothalamus and other parts of the **limbic system**, which is the subdivision of the vertebrate brain concerned with feeding behavior, homeostasis, and emotion. In the course of evolution, this pathway from the medulla through the pons to the limbic system probably represents a more primitive organizational scheme that was retained as other parts of the vertebrate brain became more elaborate. In organisms with more highly developed

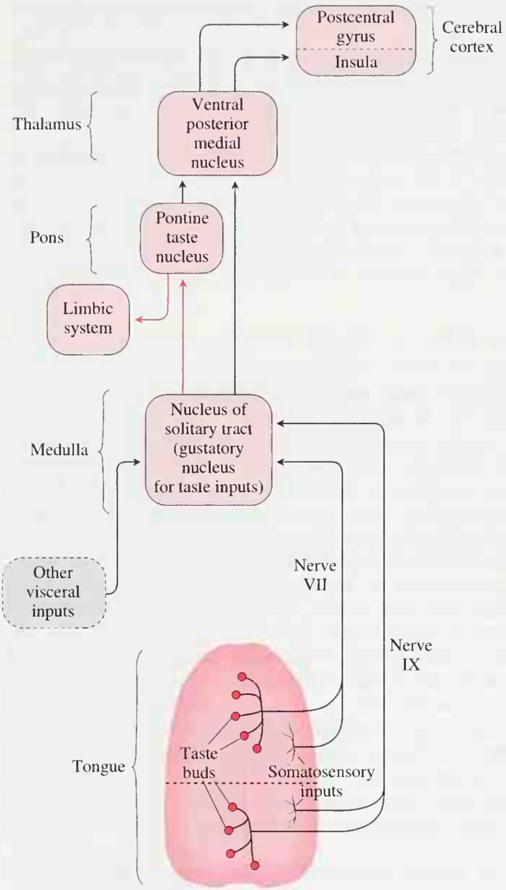


Figure 19.8
A schematic diagram of the taste sensory pathway in the central nervous system. The red arrows indicate the pathway to the limbic system, and the black arrows indicate the pathway leading to the cerebral cortex.

forebrains, the pontine taste nucleus also provides input to the thalamocortical pathway for taste perception.

In animals with the most highly developed thalamocortical sensory systems (such as primates), ascending axons from the nucleus of the solitary tract target a second location. Rather than projecting indirectly to the thalamus via the pontine taste nucleus, the ascending axons from the gustatory nucleus project directly to the thalamic nucleus concerned with sensory signals from the tongue, the **ventral posterior medial nucleus** (see Fig. 19.8). As in the nucleus of the solitary tract, the somatosensory inputs and the taste inputs from the tongue are both represented in the ventral posterior medial nucleus of the thalamus, but the taste inputs are spatially segregated to a specific subdivision of the nucleus.

In keeping with the usual organization of the somatosensory pathways, the thalamic neurons that receive information about touch, pressure, and temperature on the tongue send their axons to the primary somatosensory cortex in the **postcentral gyrus** (see chapter 15). These inputs follow the somatotopic organization within the primary somatosensory cortex, projecting to the most lateral part of the gyrus, where the other inputs from the face and head are found (Fig. 19.9). Once again, the sensory information from the

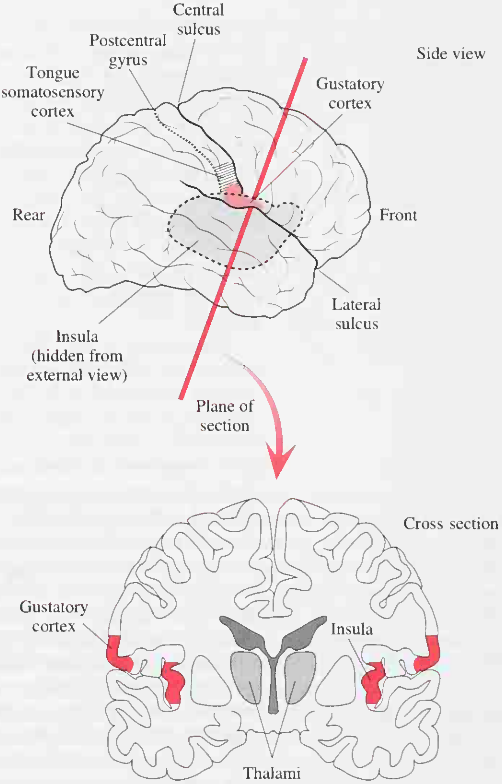


Figure 19.9
The locations of the cortical areas concerned with processing taste sensory information in the human brain. A side view is shown above, and a cross section is shown below.

taste buds remains separate from the tongue somatosensory information in the cortex. Two cortical regions receive axons from the thalamic neurons of the taste system: the gustatory cortex and the insula. The **gustatory cortex** is located in the postcentral gyrus, just below and slightly anterior to the part that receives the tongue somatosensory inputs (see Fig. 19.9). The **insula** is hidden from view within one of the deep infoldings of the cortical surface, the lateral sulcus (see Fig. 19.9).

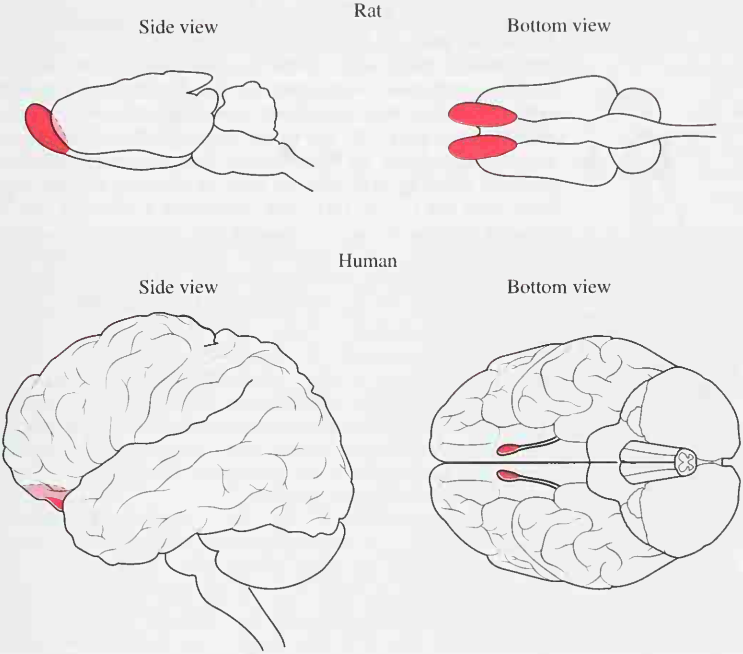
PROCESSING OF OLFACTORY INFORMATION IN THE BRAIN

Anatomical organization of the olfactory system

As noted earlier, the olfactory epithelium is located at the upper surface of the nasal passage, separated from the overlying brain by only the bone at the base of the cranium. The olfactory receptor cells themselves—which actually receive and transduce the incoming sensory stimulus—send their axons directly into the brain without any intervening synaptic connections. These axons target the **olfactory bulbs**, which are finger-like projections of the telencephalon, one on each side, immediately above the olfactory epithelium. The size of the olfactory bulbs, relative to other parts of the brain, is quite large in animals in which olfaction is a major sense, such as rodents. In humans, however, the olfactory bulbs are relatively small compared with other parts of the telencephalon, reflecting humans' poor olfactory abilities. Figure 19.10 compares the olfactory bulbs of humans and rats.

The outputs of the olfactory bulbs project to a set of basal brain structures collectively called the **olfactory cortex.** These primitive cortical structures contain pyramidal cells, like the other types of cortex, but their layered structure is not as complex as the multilayer pattern found, for example, in both motor cortex (see chapter 11) and visual cortex (see chapter 17). Because these deep-brain cortical areas arose much earlier in the course of brain evolution, they are also termed the **paleocortex.** In contrast, the newer cerebral cortical areas—what we normally mean when we use the word "cortex"—are called **neocortex.** The olfactory paleocortex is subdivided into several regions that are distributed along the lower portion of the brain, including the **anterior olfactory nucleus**, the **piriform cortex**, the **olfactory tubercle**, the **amygdala**, and the **entorhinal cortex** (Fig. 19.11). These subdivisions relay olfactory information to various brain regions, although signals are primarily transmitted to two main targets. First, as with the taste system, the limbic system receives major inputs from the olfactory cortex. Second, also like the taste system, an ascending projection goes from the olfactory paleocortex to the thalamus, and from there to the neocortex. This thalamocortical projection involves the **medial dorsal nucleus** in the thalamus and terminates in part of the frontal cortex.

Figure 19.10
The location and relative size of olfactory bulbs in a rat brain (above) and a human brain (below).



Synaptic organization of the olfactory bulb

Unfortunately, little is known about the processing of olfactory information in either the limbic system or the neocortex. However, more is known about the synaptic processing of olfactory information in the olfactory bulbs. Figure 19.12 summarizes the basic structural organization of the synaptic inputs from the olfactory receptor neurons in the olfactory bulb. The axons of the receptor neurons do not terminate diffusely throughout the bulb. Instead, the synaptic terminals cluster in spherical patches called **glomeruli** (singular: **glomerulus**), which form a regular array just below the surface of the olfactory bulb. Within each glomerulus, the axons of the receptor neurons make excitatory synapses onto the dendrites of **mitral cells** and **tufted cells**, which are the output neurons whose axons project out of the bulb to the olfactory cortex. Each olfactory receptor neuron sends its axon to a single glomerulus, and each glomerulus receives the inputs of more than 1000 receptor neurons. Approximately 100 mitral and tufted cells send their dendrites into a single glomerulus, so there is more than a 100-fold convergence of receptor neurons on second-order neurons in the glomeruli.

In addition to serving as structural units, the glomeruli act as functional units of olfactory processing. Recall that olfactory transduction mechanisms involve approximately 1000 different receptor molecules, each tuned for the detection of a specific type of odorant molecule. Each olfactory receptor neuron is thought to possess only one of the many possible types of odor receptor molecules. In other words, the olfactory epithelium contains roughly 1000 different types of olfactory receptor neurons, with the cilia of each type containing a different class of odorant receptor molecule. Compare this situation, for example, with the human retina, which uses only four types of photoreceptor cells (the rods and the three cone classes). All of the receptor neurons of a particular type in the entire epithelium are thought to send their axons to the same, single glomerulus within the olfactory bulb. In Figure 19.12, for example, all receptor neurons of type A send their axons to one glomerulus, all receptor cells of type B send their axons to another glomerulus, and so on. Furthermore, a single glomerulus apparently receives inputs from only one receptor neuron class. Thus, an individual glomerulus is activated by an odor stimulus detected by a single type of olfactory receptor molecule.

Given the specificity of the connections between olfactory receptor types and glomeruli in the olfactory bulb, the presentation of a particular odorant molecule might be expected to activate only one of the 1000 types of receptor neurons and thus only one glomerulus. Although each receptor neuron has only one type of receptor molecule, single receptor neurons and single glomeruli are actually activated by more than one type of odorant molecule. Thus, each type of olfactory receptor molecule must be broadly tuned to detect odorant molecules of a particular class, rather than only a single chemical. The receptor molecules in the olfactory cilia behave as if they are equipped with receptor sites that detect some special aspect of the molecular structure of an odorant molecule, rather than the entire molecule (Fig. 19.13). If a given chemical compound has parts that can bind to two different receptor molecules, then it will activate both olfactory receptor neurons bearing those receptor molecules. If a different chemical has only one of the relevant constituent parts, then only one of the two receptor neuron types will be activated. Of course, if an odorant molecule lacks both component parts, it will activate neither receptor neuron and must be detected by some other subtype of olfactory receptor neuron. The situation is similar to that found in the taste sensory system, except that potentially hundreds of submodalities of olfaction are involved rather than the four submodalities of taste. Only by reviewing the overall pattern of activity in the different types of olfactory receptor neurons (and, hence, in the different

Figure 19.11
A schematic diagram of the olfactory sensory pathway in the central nervous system.

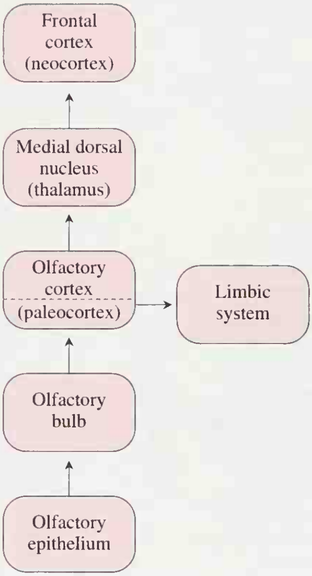
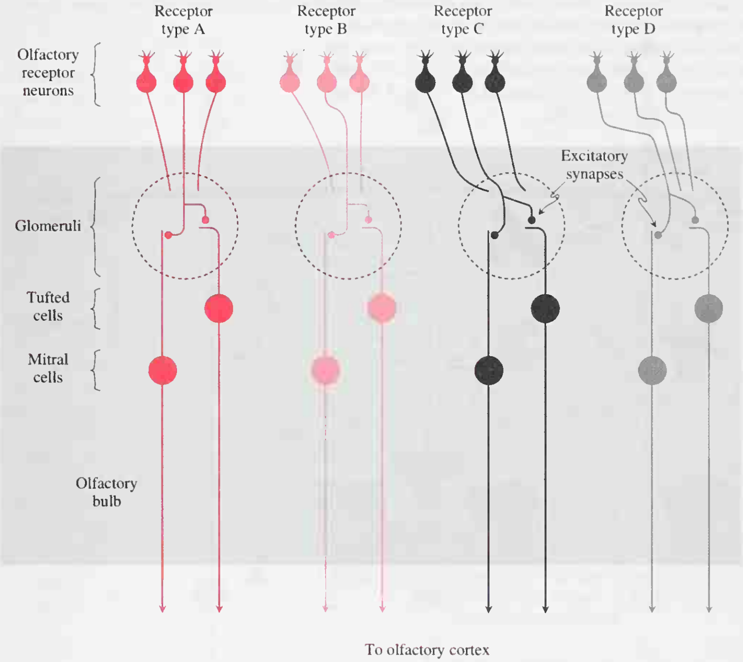

Frontal cortex (neocortex)
Medial dorsal nucleus (thalamus)
Olfactory cortex (paleocortex)
Limbic system
Olfactory bulb
Olfactory epithelium

Figure 19.12

The synaptic organization of the olfactory bulb. Four different types of olfactory receptor neurons are shown at the top (out of approximately 1000 different types). Each type projects to a single glomerulus (dashed circles) within the olfactory bulb. Within the glomerulus, the receptor neurons make excitatory synapses onto the dendrites of mitral cells and tufted cells, whose axons project out of the olfactory bulb to the olfactory cortex.



glomeruli in the olfactory bulb) can the nervous system decipher the composition of an olfactory stimulus.

As we have seen in a number of other sensory systems, lateral inhibitory interactions often represent an important aspect of sensory information processing (see chapter 14 for an overview). This holds true in the olfactory bulb as well. Two types of lateral inhibitory interneurons, the **periglomerular cells** and the **granule cells**, affect the activity of the output neurons of the bulb (the mitral and tufted cells). The synaptic connections of these inhibitory interneurons are summarized in Figure 19.14.

Figure 19.13
Olfactory receptor molecules selectively bind particular structural parts of odorant molecules. The receptor molecule on the left (type X) can be activated by any odorant molecule that has chemical structure A (shown schematically at the top) as part of its molecular structure. The receptor molecule on the right (type Y) has a different binding site, which can be occupied selectively by chemical structure B. If an odorant molecule has both structures A and B, it can bind to and activate both types of receptor molecules. Other odorant molecules (shown below) that have only structure A or only structure B will bind to one or the other type of receptor molecule, but not both. Odorants that lack both structures will not interact with type X or Y receptors; consequently, they must be detected by others of the approximately 1000 types of receptor molecules.

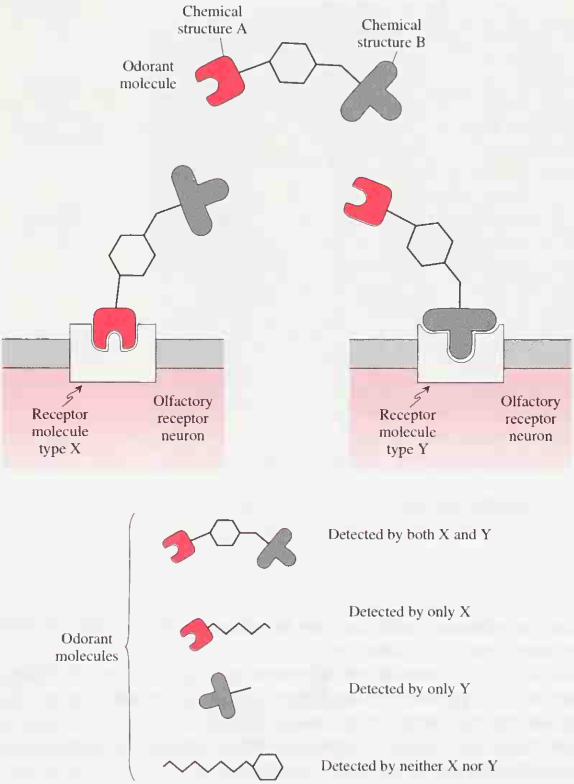
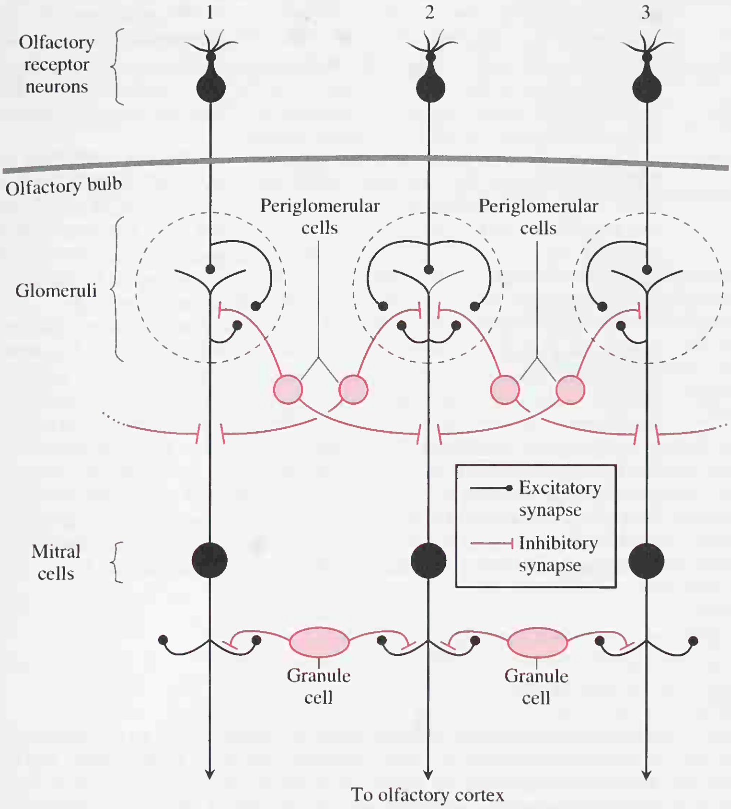


Figure 19.14
Lateral inhibitory interactions in the olfactory bulb. The two types of inhibitory interneurons appear in red. The periglomerular cells receive excitatory inputs within a glomerulus and make inhibitory synapses both within that same glomerulus and onto the output neurons of neighboring glomeruli. The granule cells receive excitatory inputs from collateral branches of the output fibers and make inhibitory feedback synapses both locally and onto neighboring output cells. For simplicity, only the mitral cells are shown for the output pathways, but similar connections are made with the tufted cells as well.



The cell bodies of the periglomerular cells, as the name implies, are located in the region around the glomeruli. Their dendrites receive excitatory synaptic inputs from the olfactory receptor neurons and from branches of the dendrites of the mitral and tufted cells within the glomerulus. In turn, the periglomerular cells make inhibitory feedback synapses onto the mitral and tufted cell dendrites in the same glomerulus. The axon of the periglomerular cell extends laterally to the dendrites of mitral and tufted cells of neighboring glomeruli, where it also makes inhibitory synapses. Thus, if the receptors feeding a particular glomerulus become excited, the periglomerular cells within that glomerulus will be excited as well. The periglomerular cells will then produce feedback inhibition within the glomerulus and inhibit the mitral cells and tufted cells of the neighboring glomeruli. This inhibitory feedback circuit in the olfactory bulb resembles the synaptic circuit formed by the photoreceptor cells and the horizontal cells in the retina (see chapter 16)—a circuit that also produces lateral inhibition.

The granule cells are located deeper within the olfactory bulb than the periglomerular cells, but they form similar inhibitory feedback connections. These cells receive excitatory synapses from output branches of mitral cells and tufted cells and make inhibitory synapses back onto the same output cells and onto the output cells of neighboring glomeruli. These connections add a second level of lateral inhibitory interaction, analogous to the lateral inhibitory effect of the amacrine cells in the retina (see chapter 16).

The lateral inhibitory connections enhance the "contrast" between neighboring glomeruli, as reported to the rest of the brain by the action potential activity in the mitral and tufted cells. Exactly how this increased contrast in activity influences the perception of odors is unclear, because it is not known how the nervous system decodes the overall pattern of activity in the glomeruli to identify odor stimuli. Nevertheless, if an olfactory stimulus activates one glomerulus more strongly than its neighbors, then the lateral connections shown in Figure 19.14 would tend to enhance the difference in activity level in the array of mitral cells connected to those glomeruli, in the same manner as described for sensory systems in general (chapter 14), the somatosensory system (chapter 15), and the retina (chapter 16).

SUMMARY

The process by which a chemical signal is translated into an electrical signal in the nervous system is called chemotransduction. In mammals, the two most important chemical senses are olfaction (smell) and gustation (taste). Chemotransduction is carried out by specialized olfactory receptor cells found in the olfactory epithelium and by taste receptor cells located predominantly in the taste buds of the mammalian tongue. Table 19.1 summarizes the transduction mechanisms in olfactory and taste receptor cells and compares them with phototransduction, which shares many features with chemotransduction.

Table 19.1 Comparison of sensory characteristics in olfaction, taste, and vision.

	Olfaction	Taste	Photoreception
Stimulus	Chemical	Chemical	Light
Direct linkage of stimulus to ion channels?	No	Yes (salt, sour) No (sweet, bitter)	No
Indirect linkage of stimulus to ion channels via G-proteins?	Yes	Yes (sweet, bitter) No (salt, sour)	Yes
Effect of stimulus on membrane potential	Depolarization	Depolarization	Hyperpolarization
Cyclic-nucleotide–gated ion channels involved in change in membrane potential?	Yes	No (sweet, salt, sour) Yes* (bitter)	Yes
Axon of sensory cell projects to brain?	Yes	No	No†

*In bitter-taste transduction, the cyclic-nucleotide–gated channels are *closed* when cyclic nucleotides bind to the channel. In olfaction and photoreception, the cyclic-nucleotide–gated channels are *opened* when cyclic nucleotides bind to the channel.

†Because the retina is already part of the brain, this entry is slightly misleading. The "No" here indicates that the synaptic output of the photoreceptor is *near* to the site of transduction, not distant as with olfactory receptor neurons.

In chemoreceptors and photoreceptors, the receptor molecules that detect the stimulus are coupled to changes in the electrical properties of the cell indirectly, via intracellular G-proteins (for taste cells, this holds for sweet and bitter tastes; salty and sour stimuli act directly on ion channels of the receptor cell). Ion channels that are directly gated by cyclic nucleotides are involved in the electrical responses of olfactory receptors, as they are in photoreceptors, and are probably also involved in the response of taste cells to bitter stimuli. In olfactory receptors, odor stimuli increase intracellular levels of cyclic AMP, which opens nonspecific cation channels and depolarizes the receptor cell. By contrast, in photoreceptors, light decreases cyclic GMP levels, which causes channels to close and hyperpolarizes the cell.

In taste receptor cells, sweet, sour, and salty stimuli do not involve cyclic-nucleotide–gated ion channels. Sweet stimuli depolarize taste cells by activating adenylyl cyclase and increasing internal cyclic AMP, which in turn promotes phosphorylation of potassium channels. The phosphorylated potassium channels close, which reduces the permeability of the membrane to potassium ions and depolarizes the cell. The stimulus for salty taste contains sodium ions, which directly enter the taste receptor cell through open sodium channels and depolarize the cell. Sour taste is elicited by increased acidity (increased proton concentration) in the saliva. The protons enter and block potassium channels, which depolarizes the taste cell.

In the mammalian brain, both the gustatory and olfactory sensory systems provide inputs to the limbic system, which is a primitive part of the brain controlling feeding and reproductive behavior, emotion, and homeostatic functions. In addition, both taste and olfactory information projects via the thalamus to the cortex, where conscious perception and identification of odors and flavors takes place. In addition, both systems encode the identity of a particular chemical stimulus via the overall pattern of activity stemming from the different subtypes of primary receptor cells, rather than via the specificity of the receptor cell exclusively for one particular type of chemical stimulus. In this regard, the chemical sensory systems are analogous to the color vision system, in which outputs originating from the three types of cone photoreceptors must be compared in the brain to establish the color of the stimulus.

PART V

Neuronal Plasticity

In the first four parts of this book, we devoted our efforts to understanding some of the basic cellular properties of nerve cells and to the neuronal circuits that allow the nervous system to do useful things for the organism. We have typically viewed the neurons and the circuits into which they are organized as static objects whose properties remain fixed. One hallmark of the nervous system is, however, its ability to alter its own circuitry—that is, to change the processing of information over time. In broad terms, this capability is referred to as plasticity in the nervous system. In Part 5, we will turn our attention to selected aspects of neuronal plasticity.

Perhaps the ultimate neural plasticity is represented by the dramatic changes that occur during the embryonic development of the nervous system. From a few precursor cells, an entire nervous system arises containing thousands of different kinds of neurons wired into a marvel of intricate detail. Although we know little about how this transformation occurs, inroads have been made into some molecular mechanisms underlying important pieces of the process. Chapter 20 describes some of these mechanisms of neuronal genesis, growth, and differentiation, emphasizing cellular communication systems whereby neurons and non-neuronal cells send signals that guide development.

The other major form of neuronal plasticity is more subtle, because it is not associated with dramatic changes in structure like those that occur during nervous system development. These changes in the nervous system underlie the day-to-day modifications of behavior that take place in even simple organisms, reflecting their experience in interacting with the environment. These behavioral events are usually referred to as "learning," and the retention of these changes is called "memory." One of the guiding principles in our approach to the nervous system is that changes in behavior must ultimately reflect changes in the cellular properties of the neuronal circuits that give rise to the behavior. In a sense, this guiding principle is the foundation for any cellular approach to the nervous system. Chapter 21 focuses on the cellular mechanisms of synaptic plasticity. Particular emphasis is given to special examples that allow cellular principles to be applied to behavioral changes that accompany learning and memory.

In Part 5, students will find that the level of understanding of underlying mechanisms is perhaps not as deep as for some aspects of neurobiology encountered earlier in this book. Put simply, we know less about the genesis of the nervous system and about learning and memory. Progress is taking place very rapidly, however (perhaps because we know less). Students should view the material here as a starting point and a guide toward the many new discoveries that will undoubtedly have come to light in the interval between the writing of these words and your reading of them. As elsewhere in this book, our approach relies on considering selected examples of neural plasticity in some detail. The examples illustrate some general principles that can in turn be used to organize new findings about the development of the nervous system and about learning and memory.

20

Neural Development

Throughout this book, we have encountered numerous examples of neuronal circuits. They have ranged from the simplest spinal reflexes, such as the patellar stretch reflex, to more complicated synaptic interconnections involved in motor pattern generation or in sensory information processing. If even the simplest neuronal circuit is to function properly, a precise set of cellular connections must be made among the cells in the circuit. Until now, we have focused on understanding the adult form of the wiring diagram in each case, without considering how it reached that form. In this chapter, we will approach the fundamental question of how the circuit wiring was established when the nervous system arose during development. Unfortunately, we are as yet unable to produce a complete answer to this important question. Nevertheless, much information is available about neuronal growth, differentiation, and the formation of appropriate synaptic connections.

The complex process of nervous system development can be divided into four broad stages. First, the precursor cells of neurons must divide and proliferate to produce the cellular raw material of the nervous system. This stage of neuronal specification and proliferation is called **neurogenesis.** Second, the newly produced neurons must move from their birthplace to their appropriate location within the overall plan of the nervous system. This dispersal is called **neuronal migration.** Third, the cell body of the neuron must grow dendrites to receive inputs from other neurons and an axon to connect with the appropriate targets. This stage, known as **process outgrowth,** is related in some ways to the migration of the cell body in the second phase. Fourth, after the axon has reached the target site, it must recognize the desired target cells and form a synaptic connection. This stage is called **synapse formation.** We will consider each of these stages in turn in this chapter.

NEUROGENESIS

Neuronal determination

In chapter 2, we briefly considered some of the early embryonic events in the generation of the nervous system. Viewed from the perspective of developmental biology, the production of a nervous system is merely one example (albeit a particularly complex one) of the sequential steps of determination and differentiation, which are required to generate any organ system. As a fertilized egg divides and gives rise to an embryo, some progeny cells are targeted to give rise to internal organs, some to muscles, and still others to the skin. Among the latter group, a subpopulation of cells becomes specified early on to give rise to the neurons and glial cells of the nervous system. This cellular targeting process is **determination.**

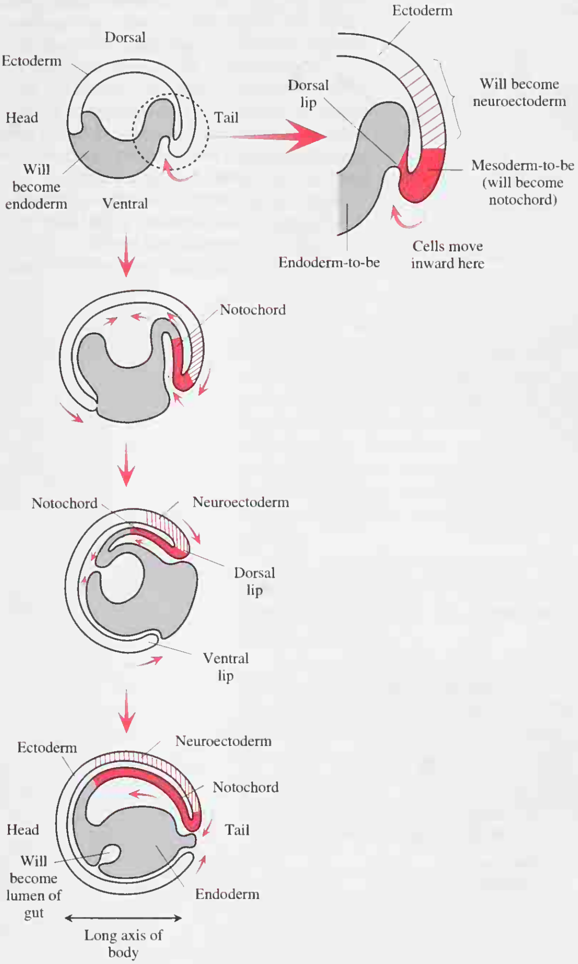
Vertebrate embryos have three cellular layers: an inner layer called the **endoderm;** a middle layer called the **mesoderm;** and an outside layer called the **ectoderm.** These layers form via a complex infolding of the single-layer early embryo, a process called **gastrulation** (Fig. 20.1). The nervous system arises from a portion of the ectoderm called the **neuroectoderm.** The selection of part of the ectoderm to become neural tissue occurs during gastrulation, as the cells of the mesoderm migrate inward beneath the ectoderm. In a process known as **neural induction,** the mesodermal cells send a signal to the cells of the overlying ectoderm, inducing them to form the **neural plate,** which will give rise to the nervous system.

An important structure formed by the mesoderm is the **notochord.** This long, rod-shaped group of cells forms along what will become the midline of the organism and defines the longitudinal axis of the body plan (see Fig. 20.1). The neuroectoderm is induced in the part of the ectoderm lying over the forming notochord. Thus, the notochord plays an especially important part in neural induction, as has been established by experiments like that illustrated in Figure 20.2. In the experiments, a small piece is removed from the ectoderm of an early-stage embryo before gastrulation, from the region of the dorsal lip that will give rise to the notochord during gastrulation. This piece is transplanted into another early embryo, where it develops into a second notochord at a position where no notochord is usually present. When the recipient embryo undergoes gastrulation, it produces its own notochord at the normal position, in addition to the transplanted notochord. In such an embryo, two neural plates will be induced, both of which will go on to form neural tubes. Thus, under the influence of the transplanted notochord, ectodermal cells that would normally produce skin tissue can be induced to form neural tissue (see Fig. 20.2). The portion of the dorsal lip that induces the development of neural tissue is called the **Spemann organizer,** in honor of the biologist who first performed transplantation experiments of this type.

What is the nature of the inducing signal that travels from the notochord to the overlying ectoderm? Neural induction does not require direct physical contact between the ectoderm and the underlying notochord, which indicates that a diffusible messenger molecule is responsible. This diffusible message could be transmitted in either of two ways. First, the underlying mesoderm in the notochord region could release a molecule that diffuses to the ectoderm, where it combines with specific receptors on the ectodermal cells and activates an intracellular signal culminating in the expression of the genes required to make neural cells. In such an **inducer mechanism,** the neuronal state is viewed as being actively stimulated in cells that would otherwise become other types of tissue. Second, the mesoderm under the neural plate could suppress a signal that causes the ectoderm to develop as non-neuronal tissue. In this **suppressor mechanism,** neuronal determination is considered to be the default state for

Figure 20.1

Early stages in the embryonic formation of the vertebrate nervous system. The diagrams show a time series during the process of gastrulation. At the top, gastrulation has just begun: at the bottom, it is almost complete. Each drawing represents a section parallel to what will become the long axis of the body. In each case, the endoderm appears in dark gray, the notochord is red, the ectoderm is white, and the developing neuroectoderm is red cross-hatched. The direction of cell migration for various regions during gastrulation is indicated by the red arrows.



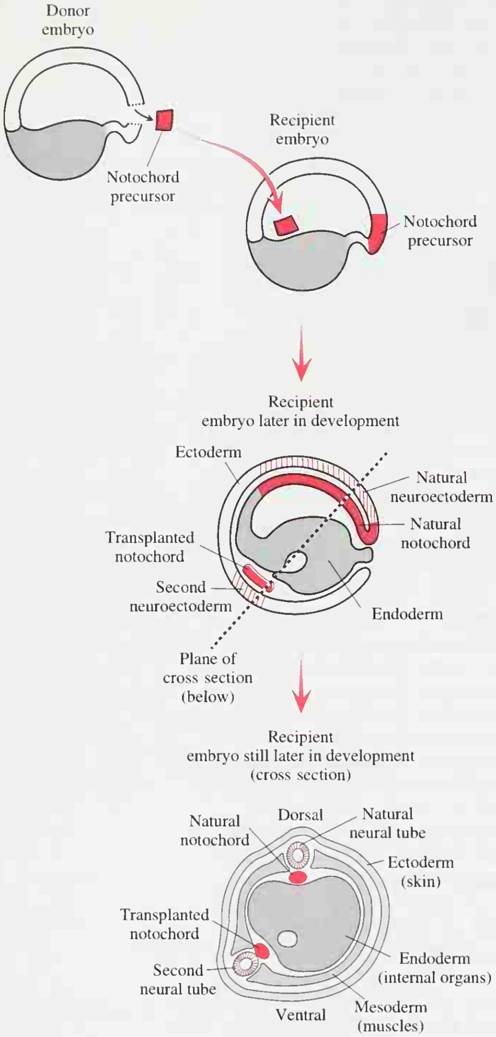


Figure 20.2
A transplantation experiment demonstrating the importance of the notochord in induction of the neuroectoderm in early vertebrate embryos. (top) At the onset of gastrulation, a piece is removed from a donor embryo at the dorsal lip, which develops into the notochord during gastrulation. The piece is transplanted inside another embryo. (middle) As gastrulation proceeds in the recipient embryo, the transplanted piece of notochord tissue is carried to a part of the embryo that normally lacks a notochord. A second region of neuroectoderm is induced by the transplanted notochord in the recipient embryo. (bottom) A cross section through the recipient embryo at a later stage of development shows the presence of two separate neural tubes. In each diagram, the notochord appears in red, and the neuroectoderm is cross-hatched in red.

ectodermal cells, which must be actively pushed down non-neuronal developmental paths by diffusible factors stemming from the endoderm. Evidence exists to support both views, and both could possibly come into play for different aspects of neural development or for different animal species. Also, there may be multiple chemical messengers involved in either type of signaling mechanism.

The suppressor mechanism is hypothesized to work in the following manner. The endoderm releases a signal protein called **activin**, which induces the formation of mesoderm by the dorsal pole of the pregastrulation embryo. If ectodermal tissue is isolated from the dorsal pole before gastrulation and placed in culture, it can be chemically induced to generate mesodermal cells via treatment with activin. As the mesoderm develops and migrates inward during gastrulation, cells of the notochord release a protein called **follistatin**, which binds to and inactivates activin. Therefore, in the vicinity of the notochord—where follistatin is released—the level of activin is reduced. The cells in the ectoderm just above the notochord are less exposed to activin and revert to their default developmental state—that is, the neural developmental path. As a result, the neural plate develops at that position, just over the notochord.

The inducer mechanism has not been elucidated as thoroughly, although it remains a topic of very active research. One candidate for an inducing factor is the protein **noggin** (so-named because it can induce excessive brain and head development when injected into frog embryos). Like follistatin, this protein is manufactured and released by the cells of the notochord, and it can induce the expression of neuronal genes in ectodermal cells. Noggin also may be involved in directing the production of muscle tissue by mesodermal cells. Most likely, noggin is only one of several soluble inducing factors released at various time points during nervous system development; it does appear to be involved in very early stages of neural induction, however.

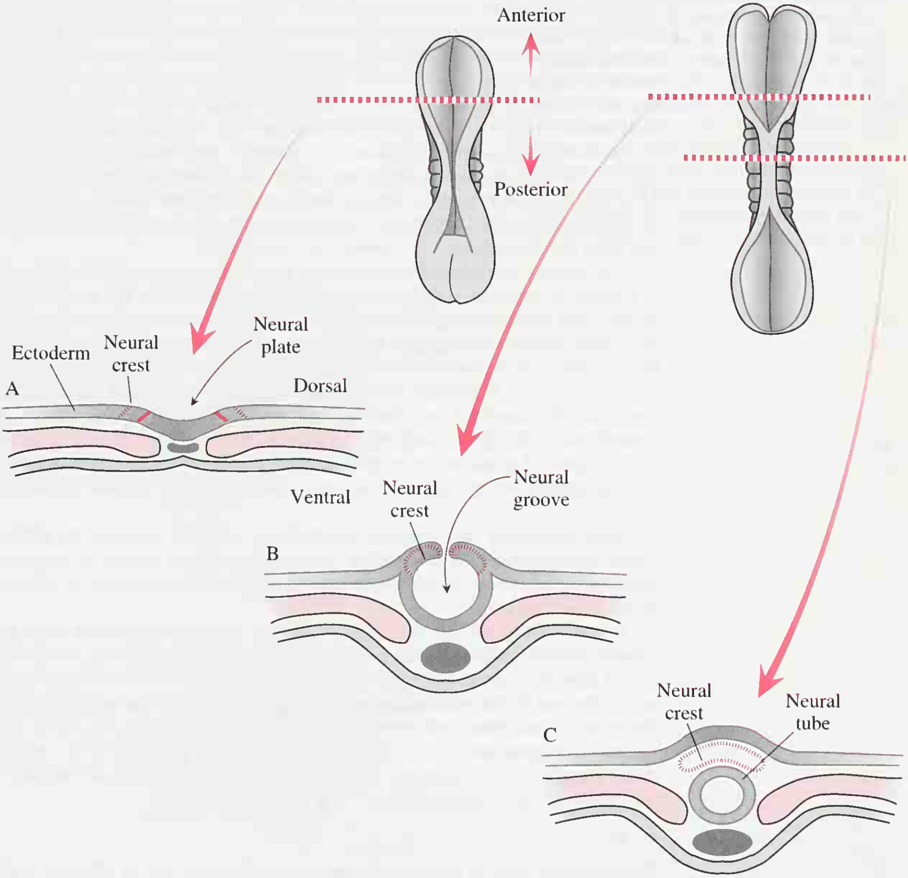
Both suppressor and inducer mechanisms may be involved in normal neural development. It is possible that suppression of activin is required, together with release of an inducer, to cause proper formation of nervous system structures.

As the cells of the neural plate proliferate, they invaginate to form the **neural groove**, before pinching off to form the **neural tube** (Fig. 20.3). The neural tube goes on to form the brain and spinal cord. At the margin of the neural groove lie the cells of the **neural crest**, which become separated from the other neural plate cells when the neural tube forms (see Fig. 20.3). The neural crest gives rise to the cells of the dorsal root ganglia, to the sympathetic ganglia, and to the rest of the neurons whose cell bodies are located in the peripheral nervous system.

Neuronal proliferation

The precursor cells of the neural tube ultimately give rise to all cells in the central nervous system. Thus, the cells of the neural tube must divide prolifically to supply the large number of cells needed in the adult brain and spinal cord. The neural tube begins as a single layer of cells and develops into a

Figure 20.3
Early differentiation of the nervous system in a vertebrate embryo. (A) The nervous system begins as undifferentiated ectodermal cells along the dorsal midline, called the neural plate. At this stage, the cells that will form the neural crest (indicated by red dashed line) lie along each side of the neural plate. (B) At a later stage, the neural plate invaginates to form the neural groove, with the neural crest located along the lips of the groove. (C) The neural groove eventually pinches off to form the neural tube, as the two opposing parts of the neural crest fuse.



structure many millimeters to centimeters thick, in the case of the human brain. Almost all of the neurons that form this thick structure arise within the neural tube itself. The proliferation of cells does not occur uniformly throughout the neural tube as it grows, however. Instead, production of new nerve cells remains localized to the inner surface of the neural tube, at the edge of the internal lumen that will ultimately become the ventricles of the brain and the central canal of the spinal cord (see chapter 2). For this reason, the region of the neural tube specialized for production of new neural cells is known as the **ventricular** zone (Fig. 20.4).

At early stages of development, the neural tube consists of only two layers: the ventricular zone where dividing cells are found, and the relatively cell-free **marginal zone** toward the outer edge of the neural tube. As the neural precursor cells of the neural tube proliferate, they repetitively go through the cell-cycle movements shown in Figure 20.4. As DNA replication proceeds in preparation for division, the cell nucleus moves outward toward the marginal zone. After DNA replication is complete, the nucleus returns to the ventricular zone. At this point, the cell is anchored via long, thin processes to the two edges of the neural tube, and the nucleus moves along these processes (see Fig. 20.4). The reason for this migration of the nucleus along the length of the cell is unknown. After the nucleus reaches the ventricular zone on its return trip, the cell retracts its long processes and divides. The two daughter cells then take one of two avenues: they reenter the cell cycle and continue to produce more progeny cells, or they exit from the ventricular zone and migrate to form the developing nervous system. The departing cells become either neurons or glial cells. Those that become neurons lose the ability to divide, while the glial precursors retain the ability to proliferate.

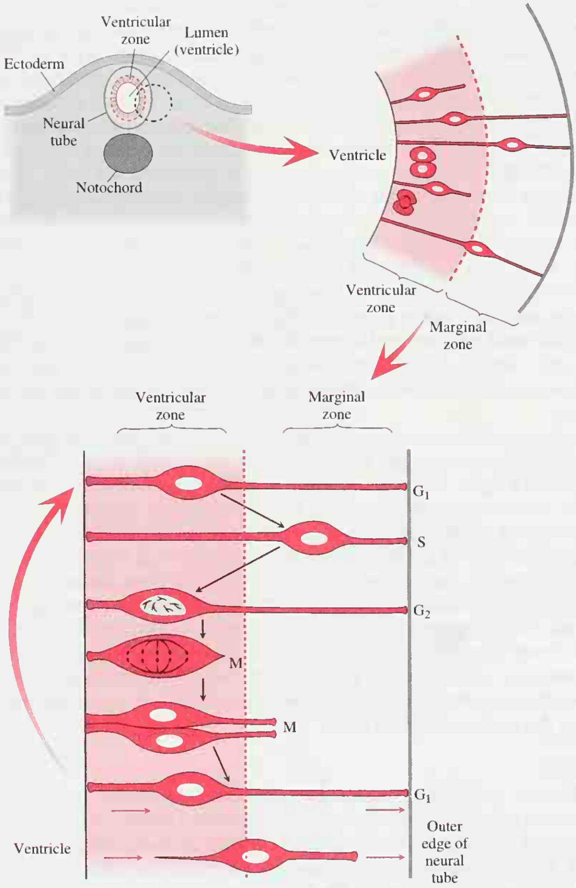
Although the ventricular-zone neuron factory produces most neurons in the central nervous system, the neurons of the peripheral nervous system have a different origin. When the lips of the neural groove fuse to form the neural tube, the neuroectodermal cells at the margin are left behind and become the neural crest. These cells generate the neurons of the dorsal root ganglia, the sympathetic ganglia, the peripheral ganglia of the parasympathetic nervous system, and the adrenal medulla. In this case, however, the precursor cells themselves move out to form the peripheral structures, generating the full complement of neural cells after they have reached their target sites in the developing body. By contrast, in the central nervous system, the dividing precursor cells generally remain restricted to the ventricular zone and the nondividing immature neurons produced there exit to occupy their positions in the brain and spinal cord.

Cell lineage

As we have seen in previous discussions, each neuronal circuit consists of several different types of neurons, each of which plays a particular functional role. The spinal cord, for example, contains motor neurons, excitatory interneurons, inhibitory interneurons, sensory projection neurons, and other neurons. At a finer level of detail, the system includes flexor and extensor motor neurons, stretch-sensitive and touch-sensitive sensory cells, and so on.

Figure 20.4

The early neural tube is subdivided into the ventricular zone, where cell division occurs, and the marginal zone. The bottom diagram shows the movements of the cell body during one cycle of cell division in a neuronal precursor cell. Moving from top to bottom, the diagrams show the cell at different portions of the cell cycle, as indicated by the letters to the right of the cell. The daughter cells can either reenter the cycle or migrate out of the ventricular zone.



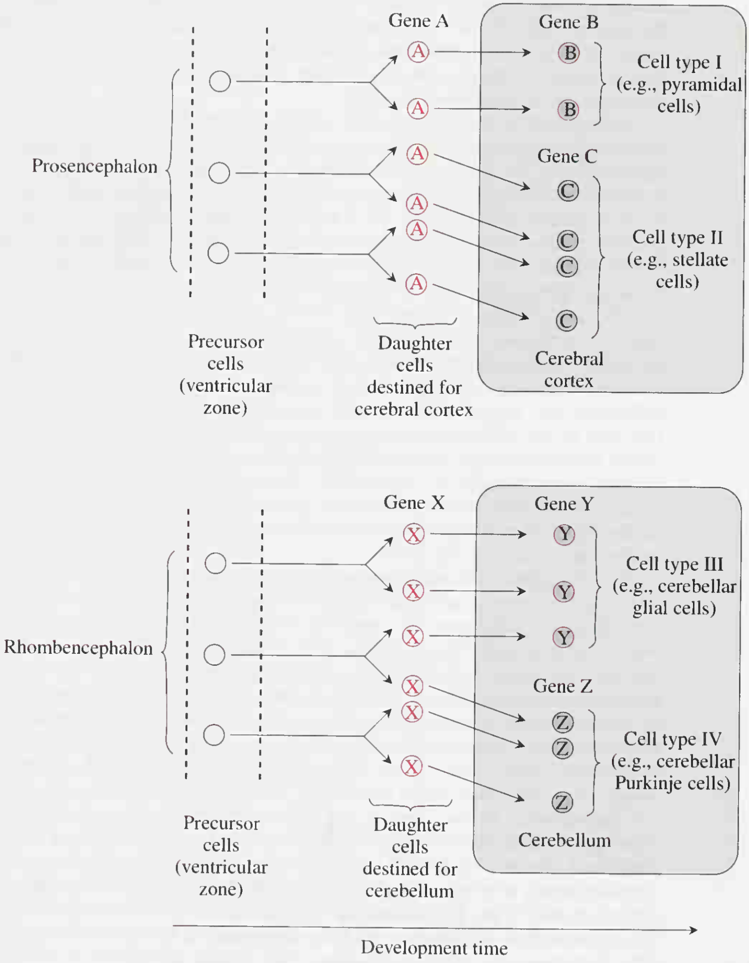
Each of these neuronal subtypes has characteristic synaptic connections and projection patterns. The heritage of every neuron can be traced back to a precursor cell, called a **stem cell**. Some stem cells give rise to a wide variety of different neuronal subtypes. In the retina, for example, a single precursor cell can have progeny among all of the different cell types of the retina, including neurons, glial cells, and retinal pigmented epithelium cells. In other cases, however, the stem cells are more restricted in scope, giving rise to only a restricted set of neuronal subtypes. In the cerebellum, for example, the output cells of the cerebellum (Purkinje cells) arise from one set of precursor cells, while interneurons within the cerebellum (granule cells) arise from a separate, distinct set of precursor cells. (We will discuss cerebellar development in more detail shortly.)

Typically, all of the cells that will become neurons of a particular type in a particular brain region arise at a specific time during the proliferation of the precursor cells. In addition, the different neuron types are generated in a fixed sequence. This sequence is thought to be genetically programmed in nervous system development, as it is in the development of other organ systems. As the neuronal precursor cells divide, different **regulatory genes** switch on and off in a programmed sequence, thereby specifying a particular neuronal subtype. The expression of different regulatory genes also follows a specific spatial pattern. For example, in the prosencephalon, the precursor cells at a particular instant in development may produce immature neurons slated for the deep layers of the cerebral cortex; at the same time, parts of the rhombencephalon may be producing immature neurons slated for the cerebellum. In this hypothetical example, the cells in the prosencephalon and the cells in the rhombencephalon express different regulatory genes that define cerebral cortical neurons and cerebellar neurons, respectively. This is depicted schematically in Figure 20.5. Under such a genetic patterning scheme, a different subset of regulatory genes would become activated later in development, driving further differentiation into specific cell types found in the adult brain (see Fig. 20.5).

The identities of the master genes that govern the regional differentiation of the nervous system and guide the production of particular types of neural cells are mostly unknown. The search for such genes is currently a very active part of neurobiology. Much of this work is based on studies of genes that control patterning of the body and nervous system in the fruit fly, Drosophila, which is a convenient and well-studied organism for genetic research. In the mammals, for example, homologues of a Drosophila gene called ***Engrailed*** are thought to control the development and differentiation of the cerebellum. Thus, "gene X" in Figure 20.5, which initiates the cerebellar lineage, may be a gene called *Engrailed-1*. The protein encoded by this gene is a transcription factor—that is, a protein that controls the expression of other genes. This theory would fit well with the proposed function of *Engrailed* as a control switch for further differentiation. Another member of the *Engrailed* family of genes, *Engrailed-2,* may influence the further subdifferentiation of cells in the cerebellum (for example, genes Y or Z in Figure 20.5). The expression of *Engrailed-1* is spatially segregated to the part of the neural tube that gives rise to the cerebellum. This spatial segregation is in turn

Figure 20.5

A sequence of expression of particular neuronal genes leads to progressively more restricted specification of cell type. This hypothetical diagram shows the fates of neuronal precursor cells generated in either the prosencephalon (top) or the rhombencephalon (bottom). The cells at the top express one set of genes appropriate for cerebral cortical neurons; the cells at the bottom express a different set of genes appropriate for cerebellar neurons.


Gene A
Gene B
Cell type I (e.g., pyramidal cells)
Prosencephalon
Gene C
Cell type II (e.g., stellate cells)
Precursor cells (ventricular zone)
Daughter cells destined for cerebral cortex
Cerebral cortex
Gene X
Gene Y
Cell type III (e.g., cerebellar glial cells)
Rhombencephalon
Gene Z
Cell type IV (e.g., cerebellar Purkinje cells)
Precursor cells (ventricular zone)
Daughter cells destined for cerebellum
Cerebellum
Development time

induced by other control genes, which probably encode transcription factors that regulate the expression of *Engrailed* genes.

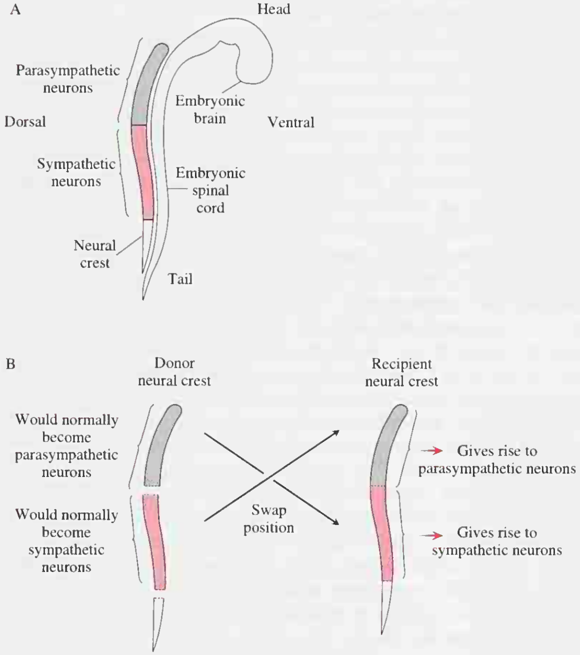
Environment also affects neuronal differentiation

To this point, we have emphasized genetic mechanisms by which the basic pattern for the nervous system is determined in early stages of the developing neural tube. In addition to these important genetic factors, however, environmental factors represent an important influence on neural development. After an early genetic switch commits a cell to a particular line of development, the cell could usually become one of several different potential cell types within that lineage in adulthood. The choice of specific cell type frequently depends on environmental factors.

Consider, for example, the developmental plasticity in final neuronal phenotype observed during the development of the sympathetic and parasympathetic neurons of the peripheral autonomic nervous system (see chapter 13). The neurons of these two branches of the autonomic nervous system arise from precursor cells found in the neural crest, which is the part of the neural plate left behind when the edges of the neural groove fuse to form the neural tube (see Fig. 20.3). Normally, the upper part of the neural crest produces parasympathetic neurons, which use acetylcholine as their neurotransmitter (Fig. 20.6A; see the portion of neural tube shaded gray). The immature neurons from this part of the neural crest migrate out to the correct locations for the parasympathetic ganglia near the peripheral target tissues and make cholinergic synapses onto the proper targets. The neurons of the sympathetic chain ganglia, on the other hand, arise from the middle portion of the neural crest (shaded pink in Figure 20.6A). These neurons give rise to the axons of the sympathetic nerves, which extend to the appropriate targets and make synapses that release the neurotransmitter norepinephrine (see chapter 13).

The parasympathetic and sympathetic portions of the neural crest can be cut out of a developing embryo and transplanted into a recipient embryo with their positions reversed (Fig. 20.6B). If the precursor cells from the anterior and middle parts of the neural crest were genetically programmed to become parasympathetic and sympathetic neurons, then the origins of the sympathetic and parasympathetic neurons would be reversed in the recipient embryo. That is, the upper neural crest would give rise to sympathetic ganglia, while the middle neural crest would generate parasympathetic ganglia. Instead, the normal pattern is maintained in the embryo receiving the reversed transplants (see Fig. 20.6B). The upper part of the neural crest still generates parasympathetic neurons, even though the precursor cells at that location were originally slated to produce sympathetic neurons. Conversely, sympathetic neurons arise from cells that would have produced parasympathetic ganglia if left in their normal positions. To achieve this end, the cells must switch their migration patterns and also switch on a different set of genes to synthesize the appropriate neurotransmitter substance. Thus, the environment of the precursor cells—not just their genetic programming—determines the migration patterns of the immature neurons, as well as the type of neurotransmitter (acetylcholine versus norepinephrine) produced by the cells.

Figure 20.6
A transplantation experiment illustrating developmental plasticity in neuronal precursor cells. (A) The normal situation. The anterior part of the neural crest (gray) gives rise to parasympathetic neurons, and the middle part (pink) generates sympathetic neurons. (B) If the positions are switched, the precursor cells behave appropriately for their new positions in the neural crest. The cells from the middle part now produce parasympathetic neurons when placed in the anterior part of the neural crest. The cells from the anterior part now give rise to sympathetic neurons when placed in the middle position.



NEURONAL MIGRATION

Movement of cells from one part of the developing nervous system to another is clearly a crucial aspect of neural development. The movement of immature neurons from their place of birth to the correct position within the three-dimensional structure of the nervous system is referred to as **neuronal**

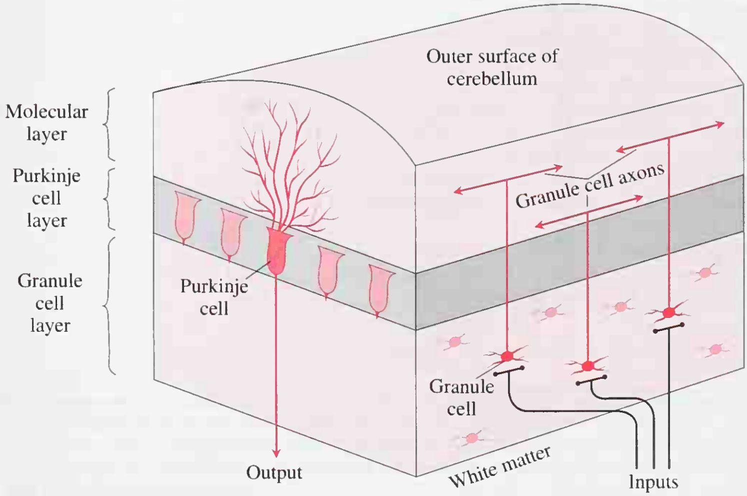
migration. In this section, we will consider some aspects of the mechanisms that guide the migrating neurons.

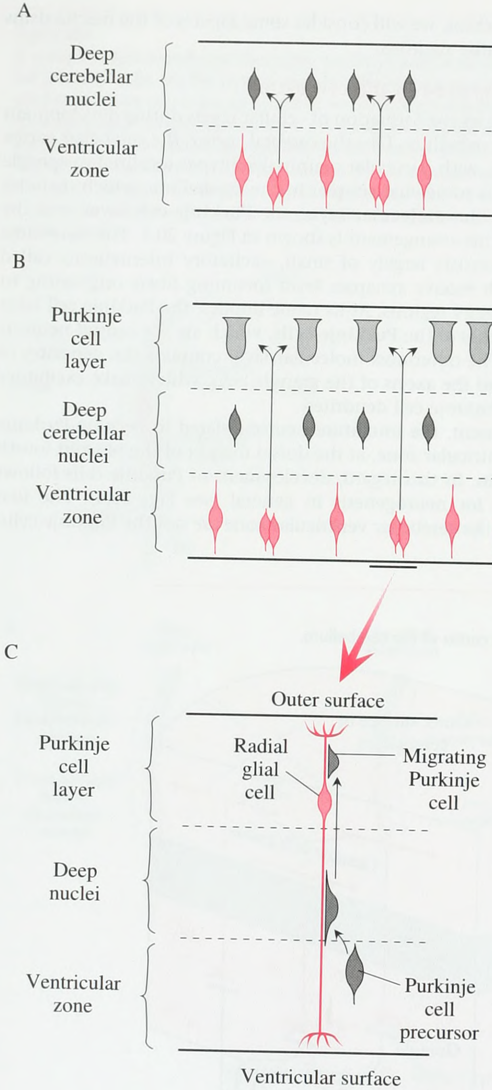
Purkinje cell migration in the cerebellum

As an example, consider the formation of cellular layers during development of the cortex of the cerebellum. Like the cerebral cortex, the cerebellar cortex is a layered structure, with particular neuronal subtypes localized to specific layers. The layering is somewhat simpler in the cerebellum, which includes three distinct layers: the **molecular layer,** the **Purkinje cell layer,** and the **granule cell layer.** This arrangement is shown in Figure 20.7. The innermost granule cell layer consists largely of small, excitatory interneurons called **granule cells,** which receive synapses from incoming fibers originating in other motor and sensory regions. As its name implies, the Purkinje cell layer contains the cell bodies of the **Purkinje cells,** which are the output neurons of the cerebellum. The outermost molecular layer contains the dendrites of the Purkinje cells and the axons of the granule cells, which make excitatory synapses onto the Purkinje cell dendrites.

During development, the immature neurons slated to become Purkinje cells arise in the ventricular zone, at the dorsal margin of the nascent fourth ventricle of the brain. In this regard, development of Purkinje cells follows the plan described for neurogenesis in general (see Fig. 20.4). The first neurons to form in the cerebellar ventricular zone are not the Purkinje cells,

Figure 20.7
The position of granule cells and Purkinje cells in the cortex of the cerebellum.




A
Deep cerebellar nuclei
Ventricular zone
B
Purkinje cell layer
Deep cerebellar nuclei
Ventricular zone
C
Outer surface
Purkinje cell layer
Radial glial cell
Migrating Purkinje cell
Deep nuclei
Ventricular zone
Purkinje cell precursor
Ventricular surface

however, but the neurons destined to make up the deep nuclei of the cerebellum (see chapter 11). These deep-nuclei neurons migrate from the ventricular zone and form a separate layer shown in Figure 20.8A. As the Purkinje cells arise in the ventricular zone, they must migrate through this layer in order to take up their appropriate positions (Fig. 20.8B). The immature Purkinje cells make this trip along a cellular highway consisting of a special class of glial cells that form early during development. These glial cells are called **radial glial cells** because they have a single, thin process that extends radially from the ventricular surface to the outermost surface of the developing cerebellum.

Granule cell migration in the cerebellum

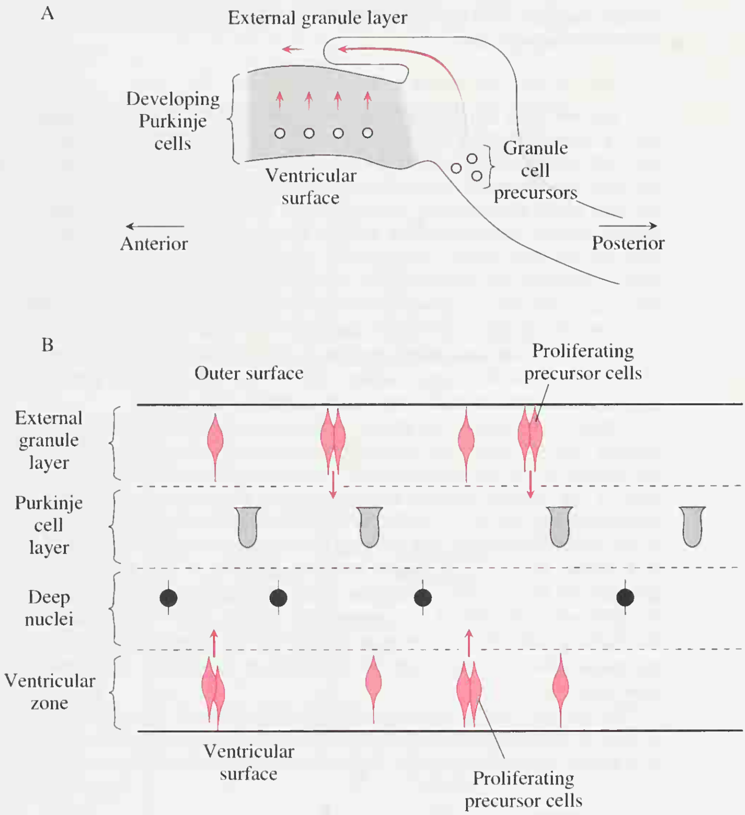
The granule cells are the last type of cerebellar neurons to be generated during development. Their genesis represents an exception to the general rule that neurons arise within the ventricular zone. The granule cells arise at the *outer* surface of the developing cerebellum, in a layer of neuronal precursor cells called the **external granule layer.** This layer is produced by proliferation of cells at the posterior margin of the cerebellum within the neural tube. As the cells divide, they spread out in an anterior direction over the outer surface of the cerebellum in the manner shown in Figure 20.9A. The immature neurons produced within the external granule layer are destined to become the granule cells in the deepest of the three layers of the cerebellar cortex. Thus, these cells must migrate in the opposite direction as the Purkinje cells, from the outer surface where they are formed, through the Purkinje cell layer, to reach their adult positions (Fig. 20.9B).

Figure 20.10 shows the stages in the development and migration of a granule cell. An immature granule neuron extends two processes parallel to the surface of the cerebellum; these processes will become the axon projection of the mature granule cell within the molecular layer of the adult cerebellum (see Fig. 20.7). Next, the cell extends a third process perpendicular to the cerebellar surface. The growing third process contacts a radial glial cell and follows the glial cell deeper into the cerebellum. The cell body of the granule cell then begins to migrate along this third process, also following the glial cell path toward the deeper parts of the cerebellum. Thus, as with the Purkinje cell, the migration of the granule cell is guided by the fibers of the radial glial cells, although the direction of movement is inward rather than outward.

The granule cell maintains very close contact with the radial glial cell during its migration. Indeed, it entwines itself around the glial cell process as it moves along, keeping the two cell membranes in close proximity. This

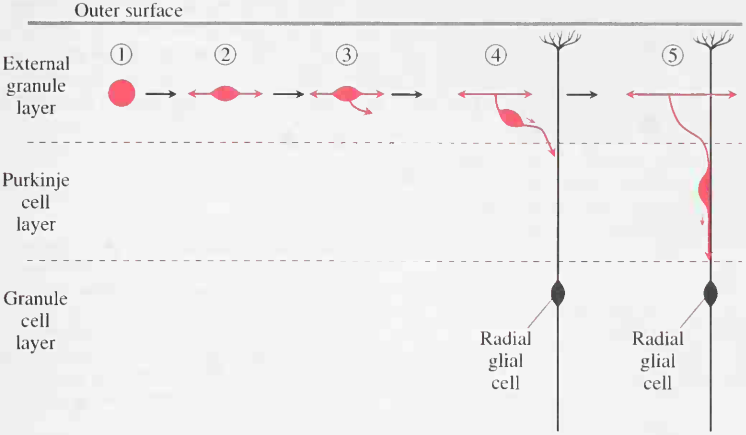
Figure 20.8
The development of cerebellar Purkinje cells. (A) The early stage in which neurons of the deep cerebellar nuclei are born and migrate out of the ventricular zone. (B) The Purkinje cells are born next and must migrate past the neurons of the deep cerebellar nuclei to reach their appropriate position. (C) The migration of Purkinje cell precursors takes place along long, thin glial cells (red) called radial glial cells.

Figure 20.9
Cerebellar granule cells originate in the external granule layer. (A) The part of the neural tube just posterior to the developing cerebellum spreads out anteriorly over the surface of the cerebellar region. (B) The granule cell precursors divide in the external granule cell layers, producing immature granule cells that must migrate through the Purkinje cell layer to reach the appropriate position.



close association of the two cells is accomplished via complementary cell-surface molecules—one on the glial cell membrane and one on the granule cell membrane—that interact strongly with one another. Because they keep the cells together, these molecules are called **cell adhesion molecules.**

Figure 20.10
Stages in the migration of a cerebellar granule cell (red). The migration occurs along the radial glial cells (black).



Many different types of adhesion molecules are known to be expressed by different types of cells throughout the tissues of the body, including the nervous system. The cell adhesion molecule in the granule cells is a membrane glycoprotein called **astrotactin.** A **glycoprotein** is a membrane protein with molecules of sugar attached at various points on the extracellular portion of the molecule. The sugar molecules may extend for great distances (on a molecular scale) into the extracellular space and are thought to provide a unique molecular surface that can be recognized by appropriate receptor molecules on target cells, providing cellular adhesion. The matching cell adhesion molecule on the radial glial cell, which interacts with the neuronal glycoprotein, has not yet been identified.

PROCESS OUTGROWTH

After a neuron has migrated to its final position within the nervous system, it must create the processes (dendrites and axons) by which it connects to other neurons and receives and sends information. Collectively, dendrites and axons are called **neurites.** Neurites often must travel long distances to reach their targets. Consider the neurons involved in the patellar stretch reflex. The motor neuron must grow an axon that connects with muscle fibers of the quadriceps muscle. To do so, the axon must move out through the ventral root of the spinal cord and navigate correctly past numerous branch points in the growing nerve before finding its synaptic target in the leg. The distance covered by the axon of the stretch-receptor sensory neuron—from the dorsal root ganglion to the quadriceps muscle via the same nerve branches as the motor axon—is also very long. In addition, the sensory neuron must send a branch of its axon into the spinal cord via the dorsal root, where it must seek out and contact the dendrites of the quadriceps motor neurons (among other synaptic targets). In this section, we will examine the mechanisms that allow growing neural processes to find their way to the proper targets.

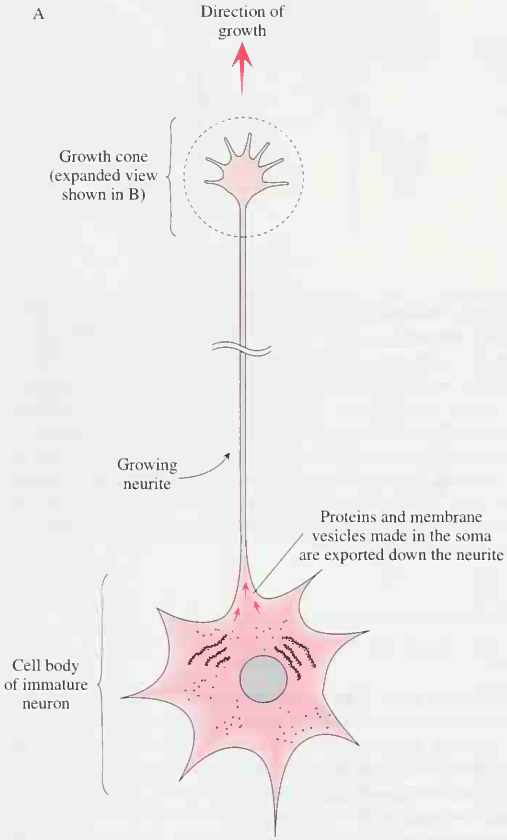

A
Direction of growth
Growth cone (expanded view shown in B)
Growing neurite
Proteins and membrane vesicles made in the soma are exported down the neurite
Cell body of immature neuron

Figure 20.11
The structure of a growth cone. (A) An immature neuron gives rise to a neurite, which extends toward its target region to either receive or transmit synaptic signals. The growth cone is located at the end of the neurite. Protein molecules and membrane vesicles are manufactured in the cell body and exported to the growth cone down the interior of the growing neurite.

The growth cone

At the leading edge of a growing nerve fiber is a specialized structure called the growth cone, which is shown in Figure 20.11. Axons may simultaneously have several growing branches, each of which contains a growth cone at its tip. The growth cone is actively mobile, extending amoeboid fingers called **filopodia** (singular: **filopodium**) that interact with the immediate environment and propel the growth cone forward. The movement of the filopodia is driven by filaments of actin, which are connected to the plasma membrane and to molecules of myosin associated with the cytoskeleton. As the filopodia at the advancing front of the growth cone extend further in the direction of movement, actin filaments are assembled at the leading edge to enable further movement. The filopodia at the trailing edge retract to allow the entire growth cone to move ahead. The actin networks of the retracted filopodia are disassembled and reused to construct new motile lattices at the

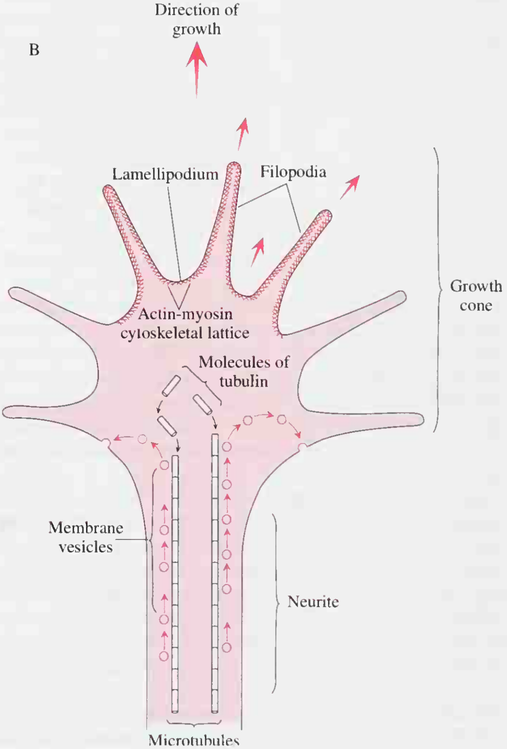


Figure 20.11 (continued)
(B) A close-up view of the growth cone. Movement of the growth cone is mediated by a cytoskeletal lattice containing two motor proteins, actin and myosin. As the neurite extends behind the moving growth cone, the microtubule backbone of the neurite is constructed from molecules of tubulin. Membrane is added via fusion of vesicles that move along the microtubules.

front of the advancing growth cone. The flattened region between filopodia, called the **lamellipodium** (see Fig. 20.11), also contains actin filaments. When an extended filopodium adheres to the substrate over which the neurite is growing, the lamellipodium moves forward to meet the tip of the filopodium. New filopodia then extend from the leading edge, and the whole process is repeated.

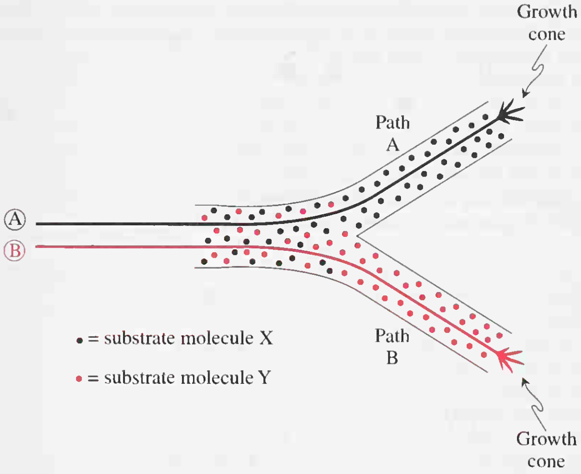
As the entire growth cone moves forward, the backbone of the neurite is continually extended so that the neurite is laid down along the path traveled by the growth cone. This backbone consists of filamentous **microtubules,** which are constructed of the protein **tubulin.** Membrane is added to the growing tip of the neurite by the fusion of vesicles, which are transported down the advancing neurite from the cell body of the neuron along the microtubules. In addition to providing membrane to the growth cone, these transport vesicles supply various membrane proteins, including ion channels, cell adhesion molecules, and membrane receptors for external chemical signals.

If the growth cone is to be able to move, it must adhere to the surrounding cells and extracellular matrix—that is, it must have traction. Adhesion is provided by cell adhesion molecules similar to those that underlie cell–cell interactions in neuronal migration. Although a wide variety of cell adhesion molecules are available, a given neuron expresses only a particular subset during process outgrowth. Thus, neurons might be able to interact with and grow upon some substrates but not others, depending on whether the substrate incorporates adhesion molecules to which the neuron's cell surface molecules can bind. In Figure 20.12, for example, neuron A has adhesion molecules that can interact with substrate molecule X, but not substrate molecule Y; neuron B has different adhesion molecules that can bind to Y, but not X. If a path consists of cells or extracellular matrix structures that have both molecules X and Y, then the neurites of both neurons can grow along that path. If the path diverges, with molecule X found only on one path and molecule Y only on the other, then the growth cones of the two neurons will also diverge and follow the paths to which they can adhere. If the branches represented branching of a peripheral nerve, for example, leading to two separate muscles, this type of mechanism could allow motor and sensory neurons targeted for one of the muscles to separate from the neurons targeted for the other muscle.

Families of cell adhesion molecules

The specific adhesion of neurite growth cones to particular pathways can be mediated via cell-to-cell interactions (as with the migration of cerebellar neurons along radial glial cells) or via interactions between the growth cone and the extracellular matrix. The **extracellular matrix** is a ubiquitous external material found in almost all tissues. It is secreted by the cells that make up the tissue and, in some cases, by specialized cells such as fibroblasts. The two main classes of macromolecules that provide the structural integrity of the extracellular matrix are **collagen**, which is a protein, and **glycosaminoglycans**, which are large polysaccharide molecules that often combine with proteins to form **proteoglycans.** The extracellular matrix also contains gly-

Figure 20.12
Cellular pathfinding during neurite outgrowth depends on the ability of cellular adhesion molecules of the growing neurite to combine with substrate adhesion molecules. Neuron B (red) can adhere to substrate molecule Y (red dots); neuron A (black) can adhere to substrate molecule X (black dots).

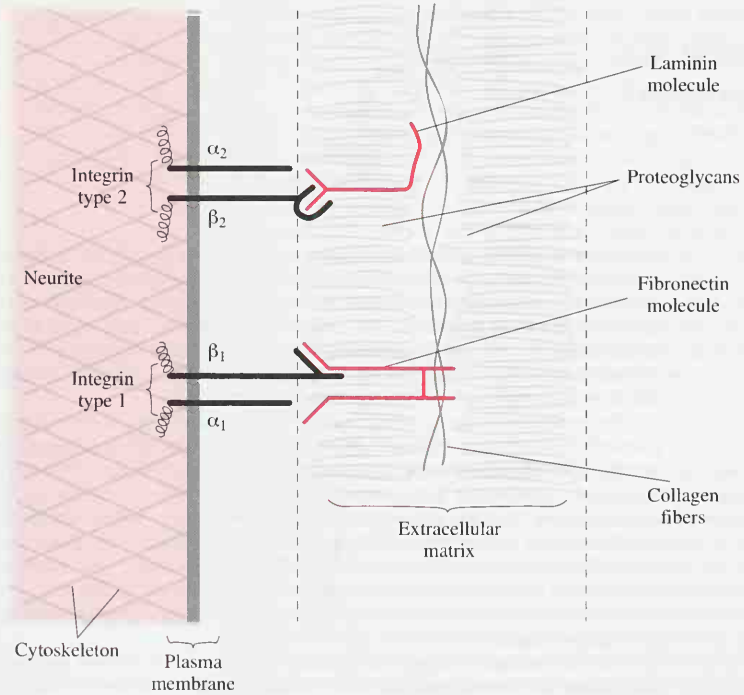


coprotein molecules, which may be the targets for the membrane adhesion molecules of growing nerve fibers. Two important glycoproteins of the extracellular matrix are **fibronectin** and **laminin**, both of which promote adhesion of cells to the matrix. **Tenascin**, another glycoprotein found in the extracellular matrix, can either inhibit or promote neurite attachment and growth, depending on the type of neural cell. In addition, collagen is recognized by some types of cell-surface adhesion molecules.

The molecular make-up of the extracellular matrix is not constant in all parts of the developing organism. By varying the polysaccharide composition and the glycoprotein content of the extracellular matrix, the cells that secrete the matrix can bestow a distinct chemical "flavor" on the matrix in the various tissues through which peripheral nerves migrate. Within the developing nervous system itself, different parts of the brain and spinal cord express different types of extracellular adhesion molecules. This chemical flavor of the extracellular environment can promote or retard the growth of neurites from different subsets of neurons and thus help to guide neurites to their proper targets.

On the external surface of the plasma membrane are cellular adhesion molecules, which enable cells to adhere to one another or to the extracellular matrix. Four families of cellular adhesion molecules have been identified: the **integrins**, the **cadherins**, the **selectins**, and the **immunoglobulin superfamily.** Each family consists of a number of related proteins. Integrins, for example, are formed by the combination of two protein subunits, an alpha subunit and a beta subunit (Fig. 20.13). Several types of both the alpha and beta subunits exist, which can then associate in various combinations to produce more than 20 different kinds of integrins. Each type of integrin binds a particular set of complementary adhesion molecules in the extracellular matrix, including fibronectin and laminin. This is shown schematically for different integrins in Figure 20.13.

Figure 20.13
The interaction between cellular adhesion molecules and adhesion molecules of the extracellular matrix. Two types of integrin molecule are shown: one binding to laminin molecules and one binding to fibronectin molecules.



The immunoglobulin superfamily of cellular adhesion molecules includes molecules such as N-CAM (neuronal cell adhesion molecule) and Ng-CAM (neuronal-glial cell adhesion molecule). These molecules are involved in cell-to-cell adhesive interactions, rather than cell-to-extracellular matrix interactions. The immunoglobulin superfamily receives its name because the extracellular part of the molecule contains several repeated amino acid sequences that are structurally similar to immunoglobulin molecules of the immune system. The adhesion molecules of the immunoglobulin class are thought to bind to the same type of molecule when they encounter it on a neighboring cell (Fig. 20.14). Thus, an N-CAM molecule binds to another N-CAM molecule on a neighboring cell, an Ng-CAM molecule binds to another Ng-CAM molecule, and so on. The adhesion molecules of the immunoglobulin family also include extracellular regions whose structure resembles part of the fibronectin molecule of the extracellular matrix. This raises the possibility that molecules like N-CAM and Ng-CAM can bind via their fibronectin-like region to integrins (which normally interact with extracellular matrix components) on neighboring cells, as well as to other N-CAM and Ng-CAM molecules.

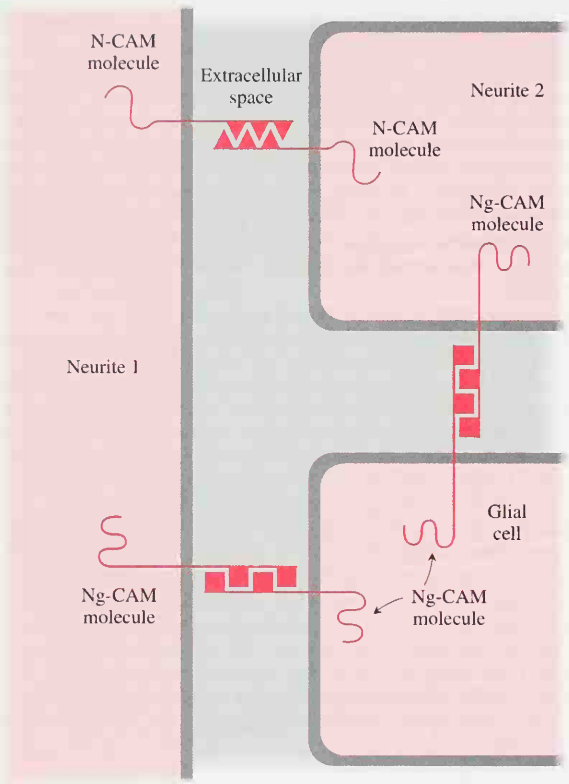
During neuronal determination, sets of genes specific for each neuronal subtype are expressed (see, for example, Fig. 20.5). Among the genes that become activated in each class of neuron are selected subtypes of the cellular adhesion molecules. Thus, the growing neurites of each neuronal class are endowed with specific adhesion molecules, which in turn govern the pathways that the neurite is able to follow as it grows. These cellular adhesion molecules are an important determinant of the migratory path taken by a newly born neuron and of the sites to which its axons and dendrites ultimately project. Although this view emphasizes the importance of genetic programming in determining neuronal differentiation and the pattern of neurite projection during development, environmental factors can also be important in final neuronal differentiation. For example, the cellular adhesion molecules may be more than just passive structural elements that provide the molecular glue to stick cells to one another and to the extracellular matrix. Adhesion molecules may also generate intracellular signals based on their interactions with the matrix or with other cells. These signals can then influence further gene expression and thus the final neuronal phenotype, reflecting the extracellular environment that the cell and its neurites contact.

Neurite guidance

Our discussion to this point has emphasized the role of molecular interactions that arise from direct contact between adhesion molecules on the surface of neurites and adhesion molecules found in the extracellular matrix or on neighboring cells. In addition to influences from these contact-mediated growth cues, the movements of growth cones are guided by molecules that are released into the extracellular space and diffuse some distance from the source to the growth cone. Such signal molecules either attract growth cones, causing the neurite to turn toward the source of the signal, or repel growth cones, causing the neurite to turn away from the source. Molecules

Figure 20.14

Cell adhesion by cell-to-cell contact. The two types of molecules (N-CAM and Ng-CAM) interact with partner molecules of the same type on other cells.



that attract are called **chemoattractants**, while those that repel are called **chemorepellents.** As a group, chemoattractant and chemorepellent molecules are known as **chemotropic molecules.** Cells that release these chemotropic signals can serve as guideposts or beacons to aid the navigation of nearby growth cones.

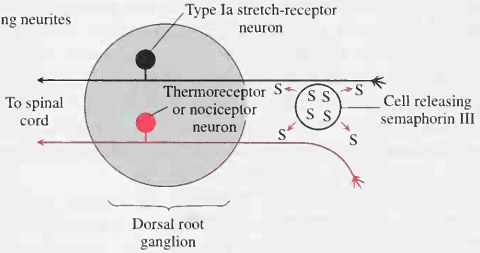
Like the cell adhesion molecules, growth-cone steering molecules secreted by cells within the central nervous system and in peripheral tissues come in a wide variety. A molecule might, for example, attract growth cones of one type of neuron, have no effect on growth cones of a second type, and repel growth cones of a third class of neuron. The functional effect of a molecule clearly depends on the type of cellular action triggered by the receptor for the molecule in the receiving neurite.

An example of this principle is shown in Figure 20.15, which illustrates the effect of the chemotropic protein called **semaphorin III** on the growth

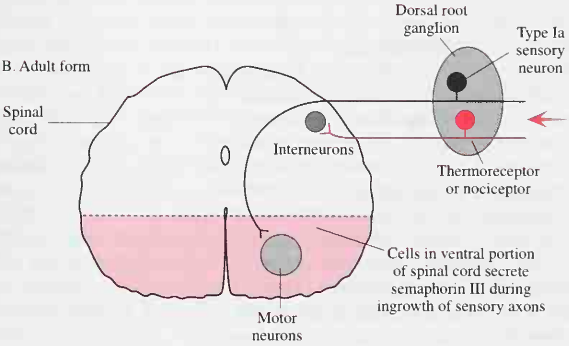
Figure 20.15

An example of axonal guidance by a chemotropic molecule, semaphorin III. (A) Growing neurites of thermoreceptor or nociceptor neurons (red) are repelled by semaphorin and turn away from a cell that secretes the signal molecule. Neurites of group Ia sensory neurons (black) are insensitive to semaphorin III and continue to grow straight past the semaphorin-secreting cell. (B) In the developing spinal cord, cells in the ventral part of the spinal cord secrete semaphorin III at the stage when sensory neurites are growing into the spinal cord. The thermoreceptor and nociceptor neurites are repelled and stay in the dorsal part of the spinal cord, where they synapse onto interneurons. The group Ia sensory neurites continue to grow into the ventral part of the spinal cord and synapse with the motor neurons there.

A. Growing neurites


Type Ia stretch-receptor neuron
To spinal cord
Thermoreceptor or nociceptor neuron
S S S S
S
S
S
S
Cell releasing semaphorin III
Dorsal root ganglion

B. Adult form


Dorsal root ganglion
Type Ia sensory neuron
Spinal cord
Interneurons
Thermoreceptor or nociceptor
Cells in ventral portion of spinal cord secrete semaphorin III during ingrowth of sensory axons
Motor neurons

of neurites of sensory neurons from the dorsal root ganglion. The neurites of group Ia sensory neurons (mechanoreceptor neurons, including the stretch-receptor neurons of stretch reflexes) are insensitive to the semaphorin protein, presumably because they lack the membrane receptors that detect semaphorin in the extracellular space. Therefore, growth cones of group Ia neurons pass by semaphorin-releasing cells without altering their direction of growth (see Fig. 20.15A). In contrast, the neurites of thermoreceptor or nociceptor neurons, which possess receptors for semaphorin III, respond by moving away from the source (that is, semaphorin III is a chemorepellent for these cells). As the growth cones of thermoreceptors or nociceptors approach the cell releasing the repellent, they change direction, taking the neurite on a path away from the guidepost cell.

In the developing spinal cord, the differential effect of semaphorin III on the two types of sensory neurons may help to arrange the projection patterns of the sensory axons (see Fig. 20.15B). Recall that the stretch-receptor axons project directly to the motor neurons of the ventral part of the gray matter in the spinal cord, where they make the direct excitatory synaptic connections that underlie the stretch reflex. The nociceptor and thermoreceptor neurons, on the other hand, synapse onto interneurons located in the dorsal part of the gray matter of the spinal cord. At the stage of embryonic development when the axons of the sensory neurons are growing into the spinal cord, cells in the ventral part of the spinal cord secrete semaphorin III. This substance repels the growth cones of thermoreceptors and nociceptors but allows the insensitive growth cones of stretch-receptor neurons to continue into the ventral parts of the cord to find their motor neuron targets. Although the sensory neurons undoubtedly use additional cues to direct themselves toward their appropriate synaptic targets, semaphorin III may well influence the adult pattern by keeping the thermoreceptor and nociceptor growth cones in the dorsal part of the spinal cord.

Semaphorin III is a member of a family of related proteins (the semaphorins) that act as chemotropic signals for the developing nervous system. Another family of chemotropic proteins, the **netrins**, also act as either attractants or repellents, depending on the nature of the receiving growth cone. Little is known about the membrane receptors in the growth cones that detect such chemotropic molecules. Likewise, the question of how growth cone motility is altered to produce changes in direction is not yet completely answered. In general, chemotropic molecules (as well as contact-mediated adhesion molecules) affect the direction of growth cone movement by differentially promoting either extension or retraction of filopodia at or near the place where a signal molecule binds to its membrane receptor. A repellent promotes retraction of filopodia; an attractant promotes extension. This effect is accomplished by changing the assembly and disassembly of the actin filaments responsible for filopodial and lamellipodial movements. The coupling between the activated chemotropic receptors and the actin filaments probably involves intracellular second messengers, including calcium ions and protein kinases, but the exact scheme has not been fully elucidated.

Neurotrophic factors

Some soluble proteins secreted into the extracellular space during development exert effects on growing neurons beyond the steering of growth cones. In fact, certain classes of secreted proteins, called **neurotrophins**, are required for the initiation of neurite outgrowth and even for neuron survival. As a result, they are often referred to as **growth factors.** Several different neurotrophins have been described, and more are likely to be discovered. These proteins are secreted by target tissues and detected by specific receptor molecules located on the membranes of the neurons that will ultimately innervate the targets. In this respect, the neurotrophins resemble the chemotropic proteins described earlier, except that much more is known about neurotrophin receptors and the cellular signals that they activate.

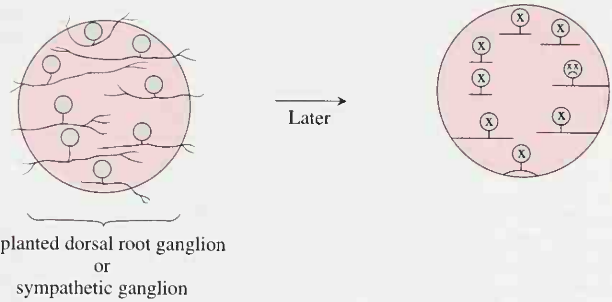
The first neurotrophin to be discovered—and the one we know most about—is **nerve growth factor** (NGF). If a small piece of a dorsal root ganglion or a sympathetic ganglion is placed in a culture dish in a nutrient medium, the neurons in the explanted ganglion will attempt to grow neurites. These neurites are feeble, however, and do not extend for an appreciable distance from the piece of ganglion. Eventually, the neurons in the ganglion will die, even though the nutrients in the artificial external medium are sufficient to support the continued survival of other types of cells. A very different situation prevails, however, if the nutrient medium includes NGF. In this case, the majority of the neurons in the ganglion survive, and neurite outgrowth is strongly stimulated (Fig. 20.16).

In addition to promoting neurite outgrowth and neuronal survival, NGF acts as a chemotropic signal for growth cones. If NGF is provided by a localized source placed to one side of the ganglion, rather than distributed uniformly throughout the medium, the growing neurites will orient themselves toward the NGF source. If the source is moved, the growing neurites will turn to follow it. NGF is secreted by a variety of target tissues that are normally innervated by sensory neurons of the dorsal root ganglia and by sympathetic neurons. Consequently, NGF may serve multiple roles in stimulating neurite growth, directing the incoming growth cones, and promoting the survival of neurons that reach the correct destination.

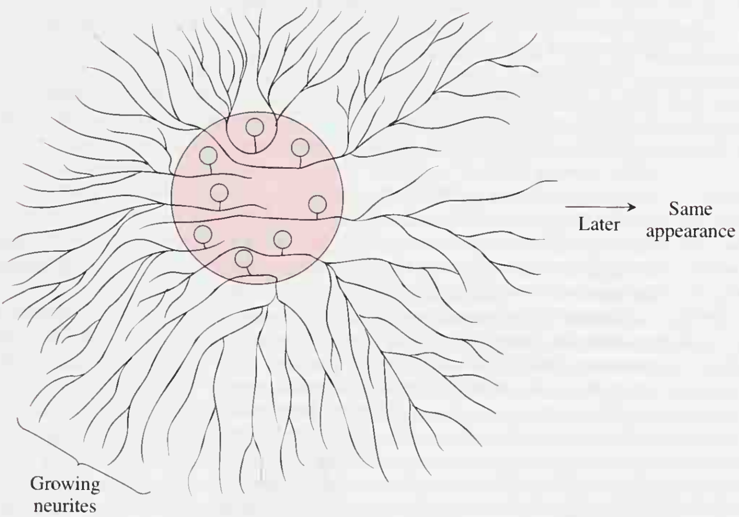
Interestingly, the early nervous system overproduces neurons. Many more neurons are produced during neurogenesis than are found in the adult nervous system. The missing cells die via a form of cellular suicide called **programmed cell death**, in which "suicide genes" are activated. The products of these genes are thought to be proteins that enzymatically attack the cell's vital machinery (including the cellular DNA itself). Why should the developing embryo generate many more neurons than needed, only to see many of the immature neurons commit suicide? The answer is uncertain, but it may relate to the difficulty of the wiring task faced by the nervous system. To ensure that sufficient numbers of neurons of each subtype reach their correct targets and form appropriate synaptic connections, perhaps an overabundance of immature neurons is necessary. However, the neurons that die are not only those whose growth cones went astray and failed to reach the

Figure 20.16
NGF promotes the survival of neurons in cell culture and the outgrowth of neurites.

A. Without NGF: poor neurite growth; neurons die



B. With NGF: prolific neurite growth; neurons survive



proper destination. A substantial loss of neurons often occurs among the population whose axons contact appropriate target cells as well.

One possibility is that programmed cell death is the default state and that neurotrophins like NGF, produced in the target tissue, prevent the activation of the programmed death sequence. If the target secretes only enough neurotrophin to support the "correct" number of incoming neurons, then the excess cells will die. Experimentally, it is possible to inject NGF into embryos, thereby rescuing the excess neurons and producing adult sensory and sympathetic ganglia with a higher-than-normal population of neurons. Conversely, it is also possible to cause abnormally high cell death—and reduced numbers of ganglionic neurons—by injecting antibodies that bind to and inactivate NGF. These findings suggest that neurotrophins do indeed influence neuronal death and survival during development.

Two other secreted proteins that are closely related to NGF also act as neurotrophins: **brain-derived neurotrophic factor (BDNF)** and **neurotrophin-3 (NT-3).** NGF, BDNF, and NT-3 have similar amino acid sequences, although they are encoded by three distinct genes that probably evolved from a common ancestral gene. Different types of neurons have different sensitivities to the three members of the NGF family. For example, within dorsal root ganglion sensory neurons, the group Ia sensory neurons that innervate the muscle spindles are sensitive to NT-3, while the nociceptor neurons that innervate the skin are sensitive to NGF. BDNF also promotes survival of certain classes of sensory neurons. For sympathetic ganglia, however, only NGF has an effect; neither NT-3 nor BDNF can mimic the effect of NGF on sympathetic neurons in culture (see Fig. 20.16).

Other neurotrophic proteins, such as **ciliary neurotrophic factor (CNTF),** are not related to the NGF family. In some cases, growth factors that were first discovered to affect the growth of non-neuronal cells also act as neurotrophins. For instance, **fibroblast growth factor (FGF)** induces proliferation of fibroblasts, but also promotes survival of various types of neurons from both the central and peripheral nervous systems. Like the NGF family, CNTF and FGF exert differential effects on various neuronal subtypes found in the nervous system. Non-protein substances can act as neurotrophic factors as well. **Steroid hormones** affect neuronal growth and differentiation in various parts of the nervous system. Although **corticosteroid hormones** are primarily involved in adrenal gland function, they also affect the development of adrenal chromaffin cells from sympathetic neuron precursors. **Sex steroid hormones** affect sexual differentiation in a variety of tissues, including the parts of the nervous system concerned with the sex organs or sexual behavior. Finally, in insects, steroid hormones (for example, **ecdysterone**) play a role in the metamorphosis from larval to adult forms. In this process, muscles and motor neurons that are used in the larva but not in the adult die as a result of increased steroid levels during metamorphosis.

Neurotrophin receptors

When a neurotrophin molecule in the extracellular fluid encounters the membrane of a neuron, it interacts with specific receptor molecules that are tuned to detect particular types of neurotrophin. When the neurotrophin binds to a receptor, the activated receptor molecule initiates a series of intracellular events, leading to complex changes in gene expression required to alter neuronal differentiation and survival. For the NGF family of growth factors, the receptor molecules are members of a family of related transmembrane proteins called **receptor tyrosine kinases** (abbreviated **trk,** which is pronounced "track"). NGF binds to a specific trk called **trkA,** BDNF binds to a different receptor called **trkB,** and NT-3 binds to **trkC.** The type of trk expressed in a neuron determines the neurotrophins to which the cell will respond during development. In addition, trk expression might be regulated by other genetic and environmental factors and could vary during the course of development, thereby contributing to neuronal subtype specification during differentiation.

The binding of NGF to the trkA receptor is shown schematically in Figure 20.17. NGF is actually formed by the combination of two identical protein subunits, which bind tightly to one another to form a **dimer.** (A dimer formed from two identical subunits is called a **homodimer.**) Each NGF subunit binds separately to a single trkA receptor molecule, bringing the two trkA molecules into close proximity. The trkA receptor is a transmembrane molecule, with an extracellular portion that binds NGF and an intracellular portion that generates intracellular signals when the receptor is occupied. The intracellular part of trkA includes a **tyrosine protein kinase** domain, which enzymatically attaches phosphate derived from ATP onto tyrosine residues in other protein molecules. In the case of the pair of trkA receptors brought together by the binding of NGF, each of the kinase domains initially targets the other trkA receptor of the pair for phosphorylation (see Fig. 20.17). The phosphorylated trkA receptor then becomes the activated form of the receptor and initiates a set of different signal cascades that culminate in such diverse responses as neurite outgrowth and suppression of programmed cell death. The only NGF-dependent step in trkA receptor activation is the formation of the receptor dimer, allowing the two partners of the dimer to phosphorylate and activate each other.

Signal paths from NGF receptors to gene expression

As might be expected from the diversity of cellular responses evoked by NGF, the activated trkA receptor affects an array of intracellular signaling mechanisms. The known signaling pathways for trkA are summarized in Figure 20.18. There are three major signal systems indicated by the three branches emanating from the activated receptor at the top of the diagram.

The best-understood pathway is that initiated by activation of the G-protein, **Ras.** A series of intermediary proteins mediate the interaction between the trkA receptor and Ras. The first intermediary is phosphorylated by the tyrosine kinase domain of trkA to start the signal sequence; the last intermediary activates Ras by replacing GDP with GTP, as occurs with other G-proteins. Ras belongs to a different class of G-proteins than the type we encountered previously in sensory systems, however. Recall that those G-proteins consist of three different protein subunits in combination and thus are called **heterotrimeric G-proteins.** G-proteins like Ras, on the other hand, consist of a single, smaller subunit and hence are called **small G-proteins.**

Figure 20.17
A schematic diagram of the interaction of NGF with its receptor molecule. (A) NGF consists of two identical protein subunits, each of which binds to a molecule of the NGF receptor, trkA. (B) The trkA receptors include an intracellular portion (red) that acts as a tyrosine kinase enzyme. The kinase attaches phosphate groups to tyrosine in proteins, including trkA. When the two trkA receptors are combined in NGF binding, they phosphorylate one another (red arrows). The phosphorylated receptor is activated and can then trigger other signal cascades.

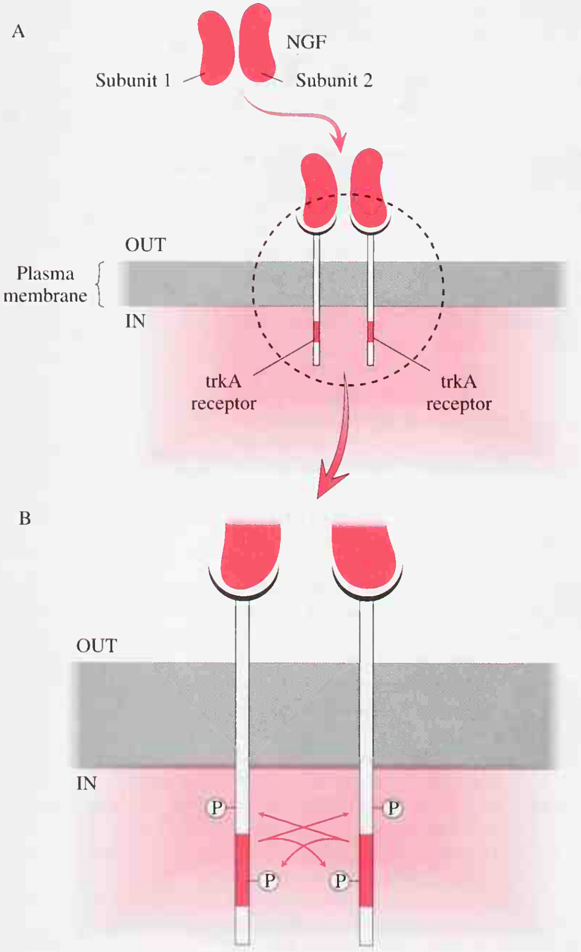
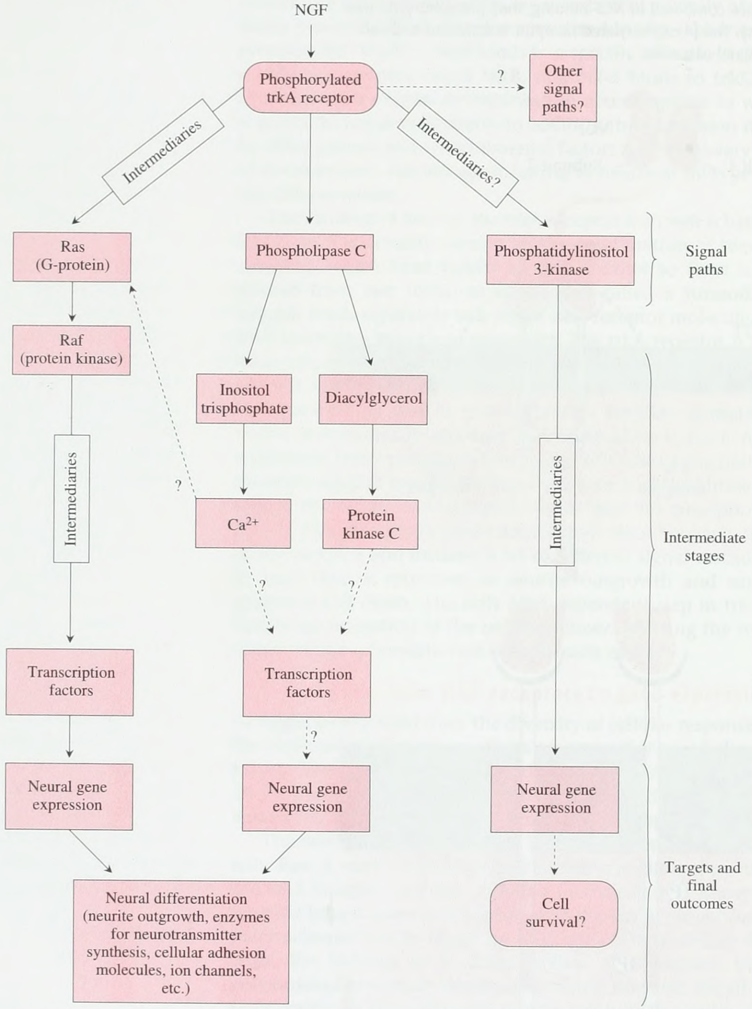


Figure 20.18
Three signal cascades triggered by the activated trkA receptor. (See the text for a full description.)



Heterotrimeric G-proteins interact directly with activated receptors, which then catalyze the replacement of GDP by GTP on the alpha subunit and the dissociation of the activated alpha subunit from the beta and gamma subunits (see, for example, the description of the rhodopsin–transducin interaction in chapter 16). In contrast, Ras and other small G-proteins are activated by **GTP exchange factors**, which are proteins that are not themselves receptors. In the case of Ras activation by trkA receptors, the GTP exchange factor represents the third in a series of three intermediary proteins that are recruited in sequence to carry the signal from the receptor to the G-protein.

The primary target for the signal cascade leading from trkA receptors through Ras is gene expression in the nucleus of the neuron. Ras, like trkA, is a plasma membrane protein; its activation is signaled to the cell nucleus via diffusible messengers. As shown in Figure 20.18, the first step in this stage of NGF signaling is the activation of a protein kinase called **Raf** by Ras. Raf triggers a cascade of kinase activation that involves a series of distinct protein kinase subtypes, with each kinase phosphorylating and activating the next kinase in the sequence. The final step is thought to be the activation of **mitogen-activated protein kinase (MAPK)**, which penetrates into the nucleus and phosphorylates transcription factors that control gene expression. The phosphorylated transcription factors bind to the regulatory regions on the DNA that initiate the transcription of a set of genes called **immediate early genes.** The proteins that are ultimately produced from the message in this set of genes are themselves transcription factors, which in turn induce the expression of a variety of genes required for neuronal differentiation (see Fig. 20.18).

The other two pathways leading from trkA receptors to neural gene expression (see Fig. 20.18) are not as thoroughly characterized as the Ras-initiated pathway. One involves direct interaction between the trkA receptor and an enzyme called **phospholipase C.** Phosphorylated trkA receptors activate the enzyme, which acts on specific types of phospholipid molecules in the plasma membrane to release two intracellular messenger molecules: **inositol trisphosphate** and **diacylglycerol.** These dual messengers operate in parallel—inositol trisphosphate increases the intracellular calcium concentration, while diacylglycerol activates a protein kinase called **protein kinase C.** Both calcium and protein kinase C can alter neural gene expression by indirectly affecting transcription factors. The third pathway, shown in Figure 20.18, involves the activation by trkA of another type of protein kinase, **phosphatidylinositol 3-kinase.** The targets for this kinase are not known, but evidence suggests that the genes activated via this pathway underlie the ability of NGF to suppress programmed cell death—and thus to promote the cell's survival.

The intracellular signaling systems activated by NGF are complicated, and our understanding of them is certainly not yet complete. This complexity is expected, however, for the intricate task of activating a wide variety of genes in the proper sequence to produce a functional neuron. Our discussion has focused on only one type of neurotrophin receptor, the trkA receptor. The other members of the trk receptor family follow similar, multiple signal paths to activate cellular responses. The situation becomes even more complex when we take into account the other types of neurotrophic factors, such as ciliary neurotrophic factor, that work via non-trk receptors. These other types of growth factors have equally complicated internal signaling schemes leading from the receptor to the genome. Unraveling these molecular signals will keep molecular neurobiologists busy for many years to come.

SYNAPSE FORMATION

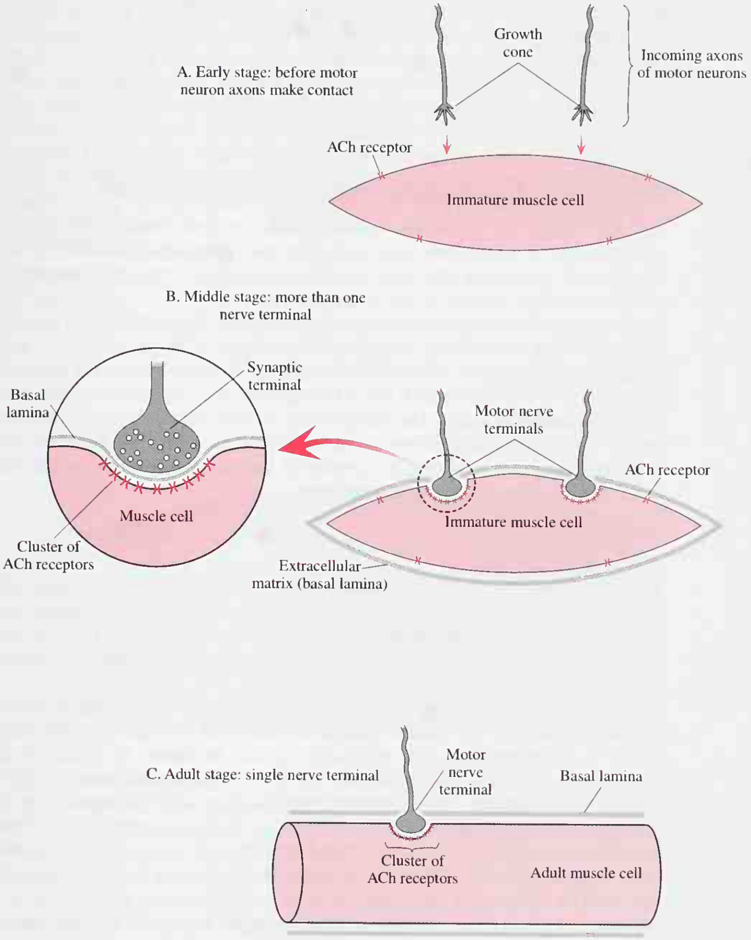
At this point, we have examined some of the mechanisms by which nerve cells are generated and then grow axons to appropriate targets, sometimes over long distances. Once the axon reaches the target, what action does it take? What are the stages involved in forming a synapse at the contact point between the ingrowing axon and the target cell? In this section, we will consider some partial answers to these questions and examine an important aspect of nervous system development: the formation of synapses. As an example, we will return to the neuromuscular junction. Recall from chapter 7 that the synaptic terminals of motor neurons release the neurotransmitter acetylcholine (ACh) at the vertebrate neuromuscular junction. Acetylcholine depolarizes the muscle cell by binding to and opening ACh receptors, which are nonspecific cation channels in the membrane of the muscle cell. The ACh receptors are clustered at the end plate of the muscle cell, just opposite the sites of ACh release from the motor nerve terminal. In this section, we will examine how this specialized synaptic contact arises during embryonic development, as the motor neuron axons grow out from the developing spinal cord and contact the embryonic muscle.

Stages of synapse formation at the neuromuscular junction

A broad overview of some important stages in the development of the mammalian neuromuscular junction is provided in Figure 20.19. When the growth cones of the motor neurons reach the muscle, the muscle cells are still in a primitive form. Even at this early stage, the muscle cells produce ACh receptors, but the receptors are inserted throughout the membrane rather than being concentrated at the end-plate region (as they are in the adult muscle). When an advancing growth cone contacts a muscle cell, forward movement and filopodial extensions halt, and the tip of the neurite begins to convert from a growth cone to a synaptic terminal. The recognition signal that triggers this conversion from motile machinery to synaptic machinery has not yet been identified, but it presumably involves interactions between cell adhesion molecules like those guiding movements during process outgrowth.

At this point, more than one neuronal growth cone contacts each muscle cell, and each growth cone begins to form a functional synaptic connection. As development proceeds, the multiple synaptic contacts from different motor neurons are eliminated, leaving the mature muscle cell with only a

Figure 20.19
The stages of synapse formation at the neuromuscular junction. (A) The growth cones of motor neurons enter the immature muscle. (B) The growth cones stop when they encounter muscle cells and begin to transform into synaptic terminals. The contact of the nerve terminal induces clustering of ACh receptors at the contact site in the muscle. Muscle cells typically receive inputs from more than one synaptic terminal at this stage. (C) The adult muscle possesses only a single synaptic input, and the ACh receptors are present almost exclusively at the end-plate region of the muscle cell.



single synaptic contact from one motor neuron. Overproduction of synapses is commonly observed during the initial stages of synapse formation throughout the nervous system. Eventually, the excess synapses are eliminated through a combination of programmed cell death and axon branch pruning, in which the surviving neurons retract some of their branches and contact fewer postsynaptic target cells. The immature neurons evidently compete for a limited number of postsynaptic target sites (one per muscle cell, in the case of the neuromuscular junction). The mechanism by which the outcome of this competition is decided is not understood.

As the synaptic connection between the motor neuron and the muscle cell consolidates, ACh receptors cluster at high density in the membrane of the postsynaptic muscle cell at the point of contact (see Fig. 20.19). At the same time, the number of ACh receptors in the non-synaptic portions of the muscle cell begins to decline. The clustering of receptors at the end plate occurs for two reasons: newly synthesized receptor molecules are inserted preferentially at the nerve contact, and previously synthesized receptors migrate to the end plate. Adult muscle contains very few ACh receptors outside the end-plate region and a very high density at the point of nerve contact. When the incoming motor neuron terminal contacts the muscle cell, the rate at which new ACh receptors are synthesized increases in the muscle cell, providing the large numbers of receptor molecules needed to achieve the high density in the adult end plate.

The muscle cell also secretes acetylcholinesterase (the degradative enzyme responsible for terminating the action of released ACh; see chapter 7) into the developing synaptic cleft. The acetylcholinesterase binds to the extracellular matrix in the cleft, which keeps the enzyme anchored in the proper spot in the extracellular space. The extracellular matrix encasing the muscle cell and synaptic terminal is known as the **basal lamina**, and at the synaptic cleft it contains components that are produced and secreted by the muscle cell and by the motor neuron terminal.

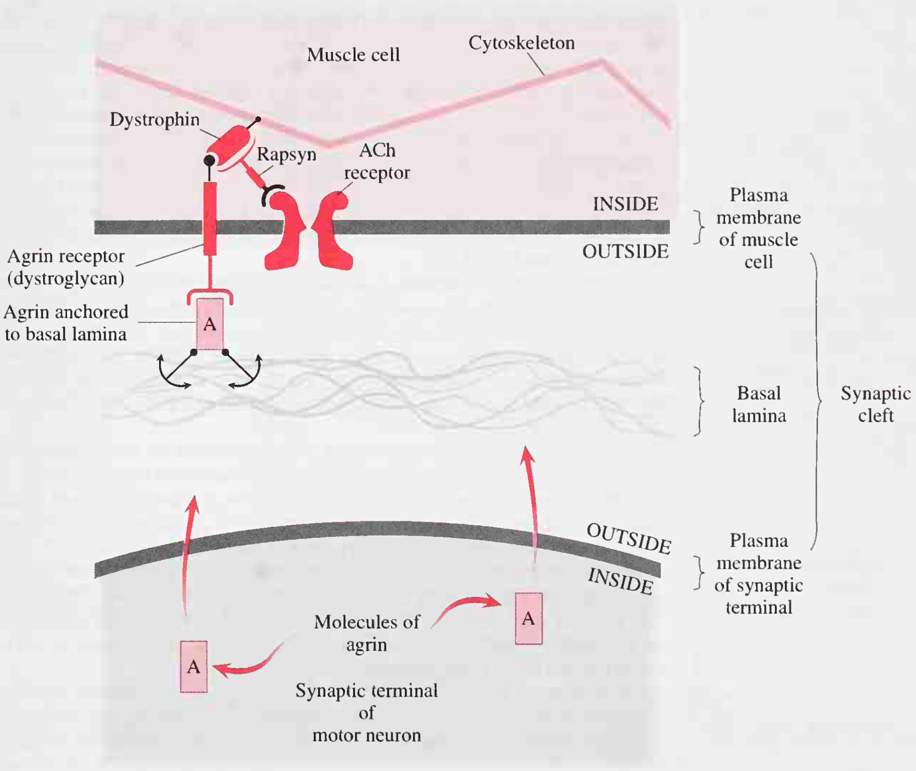
Cell–cell communication at the neuromuscular junction: receptor clustering

The ability of the nerve contact to induce changes in the muscle cell, including increased synthesis and clustering of ACh receptors, implies that some signal is sent from the nerve to the postsynaptic muscle cell. We will consider receptor clustering first, before describing the stimulation of receptor synthesis.

The clustering of receptors is triggered by a protein called **agrin**, which is manufactured by the motor neuron and secreted into the synaptic cleft, where it is incorporated into the basal lamina. As shown in Figure 20.20, agrin interacts with a special receptor molecule, a transmembrane glycoprotein in the membrane of the postsynaptic muscle cell. The agrin-receptor glycoprotein (**dystroglycan**) is connected on the intracellular face of the membrane to the cytoskeleton of the muscle cell, via a linking protein (**dystrophin**) that binds to the agrin receptor on one end and the cytoskeleton on the other. The dystroglycan–dystrophin complex also serves as a binding site for another linking protein, **rapsyn.** Rapsyn is also connected

Figure 20.20

The extracellular protein agrin anchors ACh receptors at the end plate. Agrin is secreted by the motor nerve terminal and incorporated into the extracellular matrix in the synaptic cleft. The coupling to the ACh receptor molecule is accomplished via a series of three linking proteins: dystroglycan, dystrophin, and rapsyn. These linking proteins are also connected to the cytoskeleton of the muscle cell.


Muscle cell
Cytoskeleton
Dystrophin
Rapsyn
ACh receptor
INSIDE
OUTSIDE
Plasma membrane of muscle cell
Agrin receptor (dystroglycan)
Agrin anchored to basal lamina
A
Basal lamina
Synaptic cleft
OUTSIDE
INSIDE
Plasma membrane of synaptic terminal
Molecules of agrin
A
A
Synaptic terminal of motor neuron

to ACh receptors (see Fig. 20.20). Thus, via this set of protein–protein binding, the ACh receptors become tethered to the cytoskeleton of the muscle cell on the one hand and to the basal lamina in the synaptic cleft on the other. Because the anchored ACh receptors can no longer move away from the end plate, receptors accumulate at this location as more and more are captured at the critical site. In addition, evidence suggests that agrin triggers phosphorylation of the ACh receptor by activating a tyrosine kinase in the muscle cell. The role played by this phosphorylation of the receptor remains unclear, however.

Cell–cell communication at the neuromuscular junction: receptor synthesis

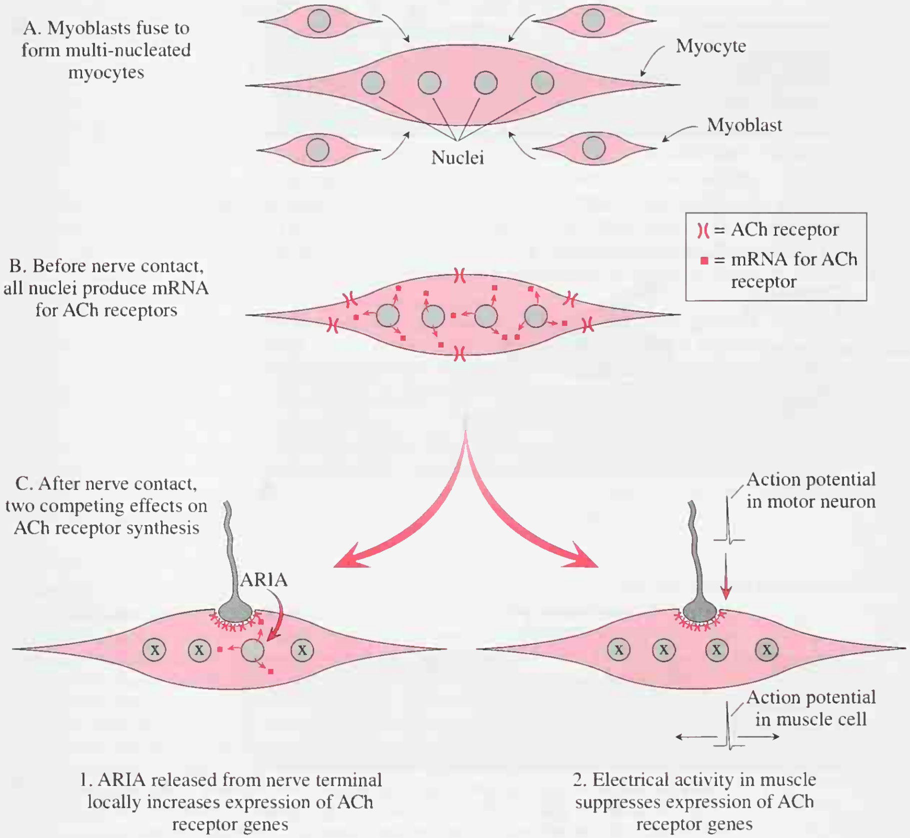
We will now turn to the increased synthesis of ACh receptors in the muscle cell induced by contact with the motor nerve. Muscle cells (**myocytes**) are long, thin cells (see chapter 9) that extend for the entire length of a specific muscle. Myocytes arise during development through the fusion of many, smaller precursor cells (**myoblasts**). Thus, a muscle cell contains many nuclei—one for each of the myoblasts that fused together to produce the muscle cell (Fig. 20.21). Each nucleus contains DNA and the machinery for gene regulation and gene transcription; thus, each can produce messenger RNA and direct protein synthesis. At early developmental stages, after formation of myocytes but before nerve contact, all of the nuclei produce mRNA coding for the subunits of the ACh receptor (albeit at a low rate). This is the period when ACh receptors are distributed uniformly throughout the surface of the muscle cell (see Fig. 20.19).

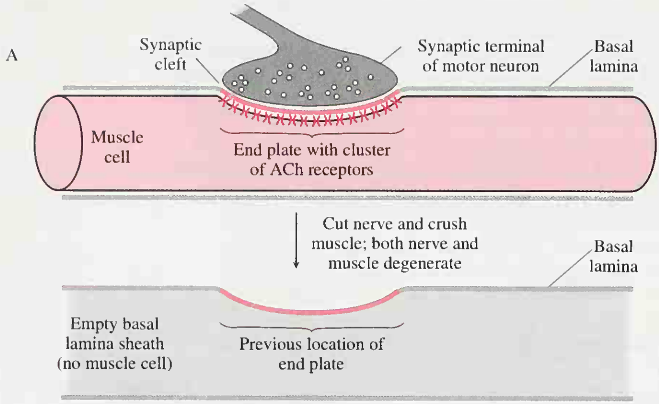
When the synaptic terminals of the motor neurons begin to form on the muscle, two changes take place. First, the onset of nerve-triggered electrical activity in the muscle cell globally *inhibits* the production of mRNA for ACh receptors in the myocyte. Second, a trophic factor released from the nerve terminals *stimulates* production of mRNA for ACh receptors in nuclei near the point of contact, locally overriding the global inhibitory effect of electrical activity (see Fig. 20.21).

The global inhibitory effect arises as a by-product of the initiation of normal synaptic transmission at the forming neuromuscular junctions. As synaptic terminals form, the agrin anchoring mechanism described earlier causes preexisting ACh receptors to cluster at the points of nerve contact. With the accumulation of receptors, ACh released from the newly formed nerve terminal in response to action potential activity in the motor neuron depolarizes the muscle fiber, stimulating action potentials in the muscle cell. The onset of electrical activity of the muscle inhibits the further production of ACh receptor mRNA in the chain of nuclei throughout the muscle cell by a mechanism that is not yet understood (see Fig. 20.21).

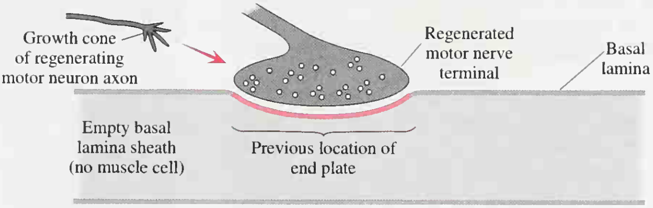
ACh receptor synthesis is stimulated locally in nuclei near the developing neuromuscular junction by the release of a protein called **ARIA** (an acronym for *a*cetylcholine *r*eceptor *i*nducing *a*ctivity) from the synaptic terminal. ARIA combines with a postsynaptic receptor tyrosine kinase and activates tyrosine phosphorylation of other intracellular signaling molecules, in a manner probably analogous to the action of NGF described earlier. In this case, the tyrosine kinase activation initiates a signal cascade that culminates in the expression of ACh receptor genes. The signal evidently has only a limited spatial spread within the muscle cell, because the activation of ACh receptor synthesis remains spatially restricted to the point of nerve contact (see Fig. 20.21). The combination of the electrically mediated inhibition of ACh receptor synthesis at nuclei outside the end plate

Figure 20.21
The stages in the modulation of ACh receptor synthesis in the muscle cell by the motor neuron synaptic terminal. (A) Muscle cells (myocytes) form by the fusion of precursor cells (myoblasts). (B) In the fused myocytes, all nuclei produce mRNA for ACh receptor proteins. (C) Contact with the nerve influences production of mRNA for ACh receptors in two ways. Action potentials (induced in the muscle cell by the activity of the motor neuron) terminate the expression of the ACh receptor genes (right diagram). The trophic substance ARIA, which is released from the synaptic terminal of the motor neuron, activates an intracellular signal cascade that locally stimulates the production of mRNA for ACh receptor subunits in nuclei near the point of nerve contact (left diagram).

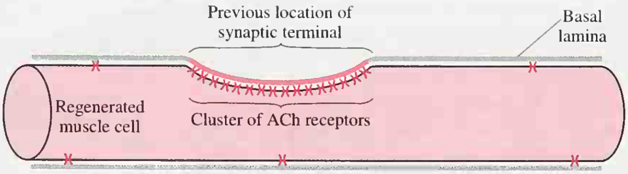

A. Myoblasts fuse to form multi-nucleated myocytes
Myocyte
Myoblast
Nuclei
)(= ACh receptor
■ = mRNA for ACh receptor
B. Before nerve contact, all nuclei produce mRNA for ACh receptors
C. After nerve contact, two competing effects on ACh receptor synthesis
ARIA
X
Action potential in motor neuron
Action potential in muscle cell
1. ARIA released from nerve terminal locally increases expression of ACh receptor genes
2. Electrical activity in muscle suppresses expression of ACh receptor genes


A
Synaptic cleft
Synaptic terminal of motor neuron
Basal lamina
Muscle cell
End plate with cluster of ACh receptors
Cut nerve and crush muscle; both nerve and muscle degenerate
Basal lamina
Empty basal lamina sheath (no muscle cell)
Previous location of end plate

B. Nerve regrows but muscle does not


Growth cone of regenerating motor neuron axon
Regenerated motor nerve terminal
Basal lamina
Empty basal lamina sheath (no muscle cell)
Previous location of end plate

C. Muscle regrows but nerve does not



and the ARIA-stimulated synthesis of ACh receptors at the end plate ensures that newly made receptor molecules are inserted into the plasma membrane near the site where they will be needed—at the developing end-plate region.

Cell-cell communication at the neuromuscular junction: muscle-to-nerve signaling

So far, we have concentrated on the signal molecules—agrin and ARIA—that are released by the presynaptic nerve terminal and act on the postsynaptic muscle cell. For effective synapse formation, however, signals must also be generated from the muscle that affect the ingrowing motor axons. For example, a "stop sign" must exist that prompts a motor neuron growth cone to cease its forward motion when it encounters an appropriate muscle cell and begins to form a neuromuscular contact. One candidate for this signal is a special form of laminin, **s-laminin**, which is manufactured by the muscle cell and secreted into the developing synaptic cleft. In the extracellular space, the secreted s-laminin becomes part of the basal lamina in the synaptic cleft. Like other cell adhesion molecules, s-laminin promotes adhesion of the motor neuron's neurite to the extracellular matrix. In addition, s-laminin inhibits neurite outgrowth, even in the presence of other adhesion molecules that stimulate outgrowth. This inhibition effectively freezes the growth cone at the point of contact with the muscle fiber, even though the surrounding environment supports growth (a necessity, because the growth cone must traverse that surrounding environment in order to reach its contact point with the muscle).

It is interesting that both agrin and s-lamina become part of the basal lamina in the synaptic cleft. Thus, after the nerve terminal and the muscle cell have produced the molecules and secreted them, the cells are no longer required to maintain the signal activity of the extracellular matrix. This rather surprising fact was demonstrated in experiments like those shown in Figure 20.22. After a neuromuscular junction has formed in frog muscle, both the nerve and the muscle can be destroyed and either (or both) then allowed to regenerate. The basal lamina remains intact when the cells are destroyed,

Figure 20.22

The extracellular matrix (the basal lamina) is important for clustering of postsynaptic ACh receptors and for localization of the synaptic terminal of the motor neuron. (A) In the adult form of the neuromuscular junction (upper diagram), the basal lamina (gray) forms a sheath around each muscle fiber. The basal lamina within the synaptic cleft (red) includes special molecular components that mediate clustering of ACh receptors and localize the nerve terminal to the correct spot. If the nerve is cut and the muscle is crushed, the motor nerve in the muscle and the muscle cells will both degenerate, leaving an empty sheath of basal lamina. (B) The nerve is allowed to regrow but regeneration of the muscle cells is prevented. The growth cones of the regenerating axons return and form new synaptic terminals at the old location of the end plate, even though the muscle cell is absent and the position is marked by only the basal lamina. (C) The muscle cells are allowed to regenerate, but the nerve is not. The muscle cells refill the basal lamina sheaths, and ACh receptors cluster at the site of the old synaptic terminal, which is now absent.

leaving behind an empty sheath of extracellular matrix (see Fig. 20.22A). When the nerve is allowed to regrow but regeneration of the muscle cells is prevented, the incoming motor axons stop growing and form presynaptic terminals at the synaptic locations that were previously occupied by the destroyed terminals (see Fig. 20.22B). This probably reflects the fact that the s-laminin previously incorporated into the basal lamina at the synaptic cleft by the now-defunct muscle cell remains in place. When the muscle is allowed to regenerate, but not the nerve, the new muscle cells refill the previous basal lamina. ACh receptors accumulate at the old synaptic site, even though the nerve is no longer present, because agrin remains in the basal lamina at the previous synaptic cleft and is still able to tether ACh receptors. Observations of this type underscore the importance of the extracellular matrix in synapse formation.

SUMMARY

The nervous system develops from embryonic ectodermal cells, which are induced to form the neural plate during the process of gastrulation. Neural induction is stimulated by a part of the mesoderm, the notochord, which underlies the dorsal portion of the ectoderm that eventually becomes the nervous system. As development proceeds, the cells of the neural plate proliferate and form a groove along the midline of the embryo (the neural groove); the edges of this groove then fuse to create the neural tube. The margins of the neural groove left behind during fusion form the neural crest, which generates the cells of the peripheral nervous system. The neural tube becomes the spinal cord and brain. Neurons are produced by division of precursor cells located at the innermost edge of the neural tube, the ventricular zone. The newly born neurons then migrate to assume their final positions within the growing three-dimensional structure of the brain and spinal cord. Neurons born in the neural crest also migrate out to the adult positions of the peripheral ganglia within the body.

As neurons of a particular type mature, neuronal genes are activated in sequence, specifying the characteristics of that cell type in increasingly finer detail. An important aspect of cell-type specification is the determination of the class of cell adhesion molecules expressed by the immature neuron. Cell adhesion molecules are used for cell-to-cell recognition and cell–substrate interactions during migration and during the growth of axons and dendrites (collectively called neurites). The tip of a growing neurite forms a growth cone, a motile structure responsible for moving the extending neurite along the proper path, guided by molecular guideposts found on cells and in the extracellular matrix between cells. In addition to cell adhesion molecules, chemotropic molecules act as diffusible messengers that either attract or repel neurons' growth cones at a distance from the source.

Neurotrophic factors are proteins that are secreted by various neural and non-neural cells and that influence neuronal survival and growth. The best-studied example of a neurotrophin is nerve growth factor (NGF), which is detected by specific neurotrophin receptor molecules in the membrane of the receptive neuron. The NGF receptor is a member of a family of receptors called tyrosine receptor kinases (trk). The activated receptor is a kinase that phosphorylates tyrosine residues on a variety of cellular target proteins. The phosphorylated target proteins serve as internal signals that initiate a series of events leading to the expression of genes appropriate for growth and for the development of neuronal characteristics.

The formation of a synapse involves signals that are sent and received by both the presynaptic cell and the postsynaptic cell. At the neuromuscular junction, the contact of the growth cone with the immature muscle cell induces clustering of acetylcholine receptors in the muscle cell membrane at the point of nerve contact. In addition, nerve contact increases the rate at which the muscle cell synthesizes acetylcholine receptors. These effects are mediated via two molecular signal proteins, agrin and ARIA, that are secreted by the nerve terminal into the developing synaptic cleft. The muscle cell secretes a special form of an extracellular matrix molecule called s-laminin into the cleft, which acts as a stop signal for motor neuron growth cones.

21

Synaptic Plasticity

Animals alter their behavior based on experience. Even animals with simple nervous systems can learn to associate previously neutral sensory stimuli with biologically significant events, learning to avoid situations signifying danger and to approach stimuli associated with reward. These behavioral changes are the external manifestation of underlying changes in the neural systems that control the behavior. Thus, the nervous system is capable of changing the strength of synaptic connections—perhaps even breaking and making synaptic contacts among neurons—based on past experience. The outcome of this learning process lasts for a long time (decades, in some cases).

How does the nervous system modify itself to support learning and memory? Few answers to this question have been found, partly because the basic circuit underlying a particular behavior must be understood before it is possible to identify the changes in the circuit accompanying learning. This understanding of underlying neural circuitry has been reached in very few instances, and then only for simple types of behavior such as reflexes. We normally envision reflexes as being fixed patterns of behavior, determined by the fixed wiring of simple combinations of neurons. In many cases, however, reflexes are adaptable on the basis of experience and show changes attributable to learning and memory. We will discuss two examples of these modifiable reflexes later in this chapter.

In the first part of this chapter, we will describe some simpler changes that occur in the strength of synaptic connections among neurons. Neurobiologists have uncovered the cellular mechanisms for various categories of these time-dependent changes in synaptic strength. Although these synaptic modifications may not have all the characteristics normally associated with learning and memory, the simpler cellular mechanisms do point toward possible ways that the nervous system might accomplish learning and memory.

SHORT-TERM CHANGES IN SYNAPTIC STRENGTH

Synaptic enhancement

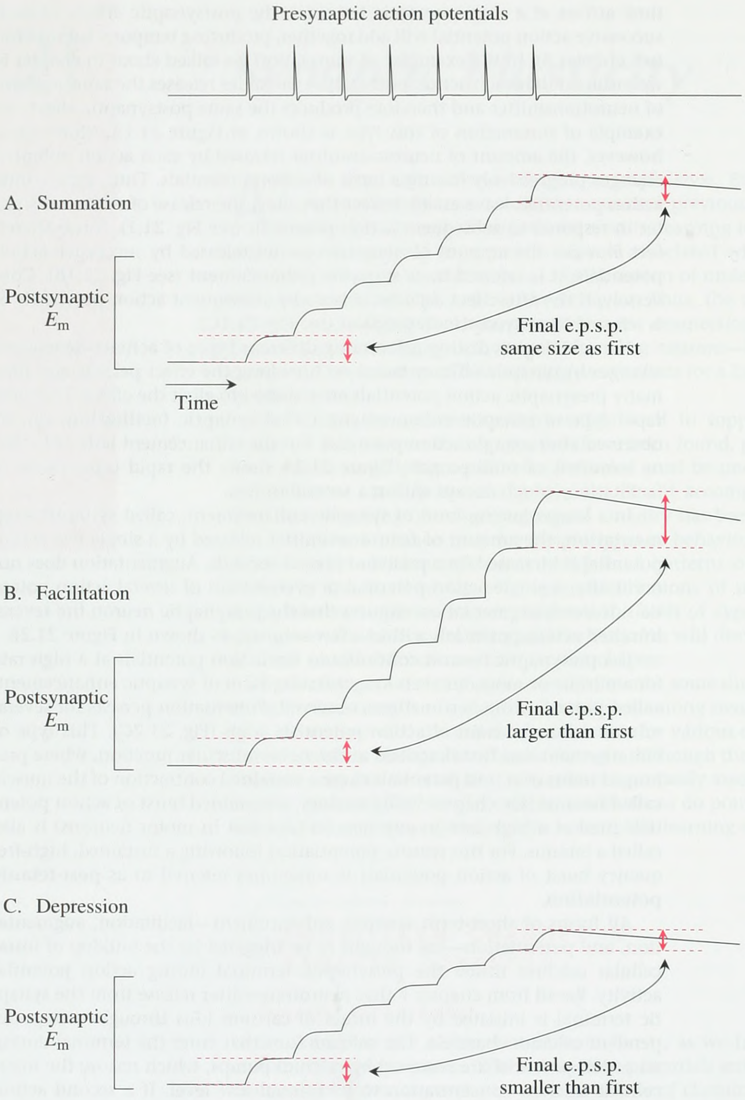
Neurons tend to fire action potentials in bursts, as we have seen in both motor and sensory systems. When the action potentials arrive at the synaptic terminals of a neuron, each one induces release of chemical neurotransmitter, which initiates a postsynaptic potential in cells receiving synaptic connections from the neuron. If a series of action potentials closely spaced in time arrives at a single synaptic terminal, the postsynaptic effects of each successive action potential will add together, producing temporal summation (see chapter 8). In the examples of summation we talked about in chapter 8, we assumed that each action potential in the series releases the same amount of neurotransmitter and therefore produces the same postsynaptic effect. An example of summation of this type is shown in Figure 21.1A. More often, however, the amount of neurotransmitter released by each action potential changes progressively during a burst of action potentials. Thus, presynaptic action potentials leave an aftereffect that alters the release of neurotransmitter in response to subsequent action potentials (see Fig. 21.1). If the aftereffect *increases* the amount of neurotransmitter released by successive action potentials, it is referred to as **synaptic enhancement** (see Fig. 21.1B). Conversely, if the aftereffect *depresses* release by subsequent action potentials, it is referred to as **synaptic depression** (see Fig. 21.1C).

Neurobiologists distinguish among different types of activity-dependent changes in synaptic efficacy based on how long the effect persists and how many presynaptic action potentials are required to elicit the effect. The most rapid type of synaptic enhancement, called **synaptic facilitation**, can be observed after a single action potential, but the enhancement lasts only tens or hundreds of milliseconds. Figure 21.2A shows the rapid time-course of facilitation, which decays within a second or less.

In a longer-lasting form of synaptic enhancement, called **synaptic augmentation,** the amount of neurotransmitter released by a single test action potential is increased for a period of several seconds. Augmentation does not occur after a single action potential or even a train of several action potentials. Instead, augmentation requires that the presynaptic neuron fire several hundred action potentials within a few seconds, as shown in Figure 21.2B.

If a presynaptic neuron continues to fire action potentials at a high rate for a minute or more, an even longer-lasting form of synaptic enhancement, called **potentiation**, is sometimes observed. Potentiation persists for several minutes after the train of action potentials stops (Fig. 21.2C). This type of enhancement was first described at the neuromuscular junction, where prolonged trains of action potentials cause a sustained contraction of the muscle called tetanus (see chapter 9). By analogy, a sustained burst of action potentials fired at a high rate in any neuron (not just in motor neurons) is also called a tetanus. For this reason, potentiation following a sustained, high-frequency burst of action potentials is sometimes referred to as **post-tetanic potentiation.**

All forms of short-term synaptic enhancement—facilitation, augmentation, and potentiation—are thought to be triggered by the buildup of intracellular calcium inside the presynaptic terminal during action potential activity. Recall from chapter 7 that neurotransmitter release from the synaptic terminal is initiated by the influx of calcium ions through voltage-dependent calcium channels. The calcium ions that enter the terminal during an action potential are removed by calcium pumps, which restore the intracellular calcium concentration to its normal low level. If a second action potential arrives while some calcium remains from a prior action potential, the calcium ions that enter during the second spike will sum with the


Presynaptic action potentials
A. Summation
Postsynaptic
E_m
Time
Final e.p.s.p.
same size as first
B. Facilitation
Postsynaptic
E_m
Final e.p.s.p.
larger than first
C. Depression
Postsynaptic
E_m
Final e.p.s.p.
smaller than first

residual calcium, causing calcium ions to accumulate inside the terminal. The time-course of removal of this calcium buildup correlates well with the time-course of the enhanced transmitter release during facilitation, augmentation, and potentiation.

Figure 21.3 shows a schematic diagram of this "residual calcium" model of synaptic enhancement. Calcium ions that enter during an action potential directly trigger the fusion of synaptic vesicles with the plasma membrane, inducing the release of the neurotransmitter content of the vesicles into the synaptic cleft. In addition, calcium ions set in motion biochemical events that potentiate the release of transmitter during subsequent action potentials. Although the identity of these biochemical events remains unknown, their activity persists—and neurotransmitter release is enhanced—as long as the calcium level remains elevated after a series of action potentials.

The synaptic enhancement just described would tend to make synapses more effective if the presynaptic neuron has recently undergone intense activity. Thus, if a postsynaptic neuron receives inputs from a variety of presynaptic cells, the presynaptic cells that have recently fired with the greatest frequency will have the greatest weight in determining the activity of the postsynaptic cell. The synaptic influence changes with time on a scale of seconds or minutes, depending on the level of activity in the presynaptic cell. As a result, neurons within a neural circuit "pay attention to" the presynaptic cells that are most active in the recent past and thus most involved in whatever aspect of behavior the organism is engaged in at the moment.

Synaptic depression

Although enhancement of synaptic efficacy during sustained activity may be desirable in some circumstances, it may be detrimental in other situations. For example, in sensory systems, the nervous system is often more interested in changes in stimulus conditions and less interested in the constant aspects of the environment. Thus, presynaptic inputs that have been most active in the recent past may receive less weight in determining the response of postsynaptic cells. This goal can be achieved by synaptic depression (see Fig. 21.1), in which the amount of neurotransmitter released by a single action potential decreases with time during sustained firing. In this way, the greatest amount of transmitter release—and hence the greatest postsynaptic response—will occur at the onset of a burst of action potentials.

Three possible mechanisms for synaptic depression are illustrated in Figure 21.4. In many synaptic terminals (especially in the central nervous system), only a limited pool of synaptic vesicles is available for rapid release

Figure 21.1

Postsynaptic responses to a burst of presynaptic action potentials, which are shown in the top trace. (A) Each excitatory postsynaptic potential has the same amplitude, and the postsynaptic response shows simple temporal summation. (B) In facilitation, the postsynaptic responses become progressively larger during the burst of presynaptic action potentials. (C) In depression, the postsynaptic responses become progressively smaller during the burst of presynaptic action potentials.

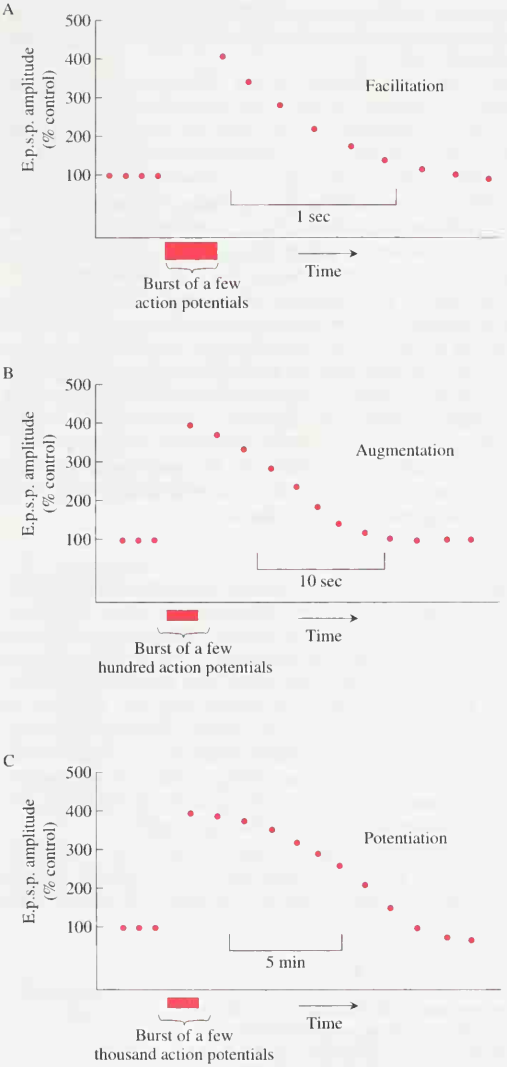
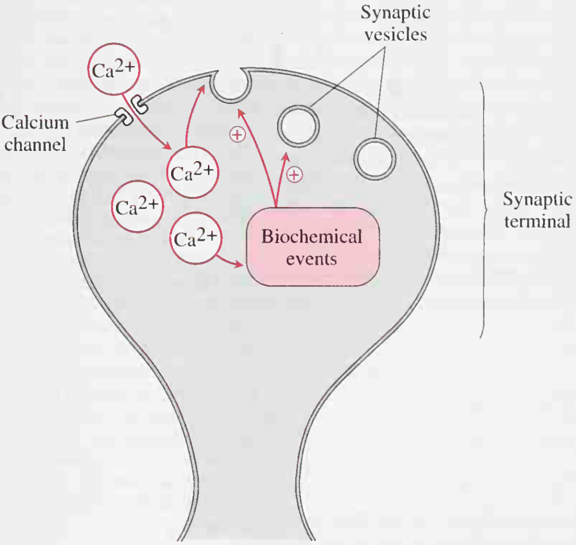


Figure 21.2
Three forms of synaptic enhancement. Each graph plots the amplitude of the e.p.s.p. elicited in a postsynaptic neuron by a single presynaptic action potential. At the time indicated by the red bar below each graph, a burst of presynaptic action potentials was given to activate synaptic enhancement. The amplitude of the e.p.s.p. is expressed as percent of the pre-enhancement baseline amplitude. (A) Facilitation is triggered by a small number of action potentials and lasts for a second or less. (B) Augmentation is triggered by a longer burst of action potentials and lasts for a few seconds. (C) Potentiation lasts several minutes after a prolonged burst of presynaptic action potentials.

Figure 21.3
Calcium ions accumulate inside the presynaptic terminal during a burst of action potentials. The depolarization produced by the action potential opens voltage-dependent calcium channels, allowing calcium ions to enter the terminal. The accumulation of calcium triggers biochemical events that potentiate the fusion of synaptic vesicles triggered by subsequent action potentials.



during action potential activity. With repetitive activity, this vesicle pool can be depleted faster than it can be replenished, causing the amount of released neurotransmitter to decline with time (see Fig. 21.4A). Other possible mechanisms for synaptic depression are based on the accumulation of calcium ions within the presynaptic terminal, as described above for synaptic enhancement. In the case of synaptic depression, the targets for the calcium are different, however, as shown in Figure 21.4B. Accumulation of calcium ions can cause voltage-dependent calcium channels to close, as described for calcium channels in cardiac muscle cells in chapter 13. This calcium-dependent inactivation of calcium channels reduces the amount of calcium entering during an action potential, and so inhibits neurotransmitter release. Intracellular calcium ions also target calcium-activated potassium channels (see chapter 5). When calcium accumulates inside the presynaptic terminal, these potassium channels open, hyperpolarizing the terminal and promoting

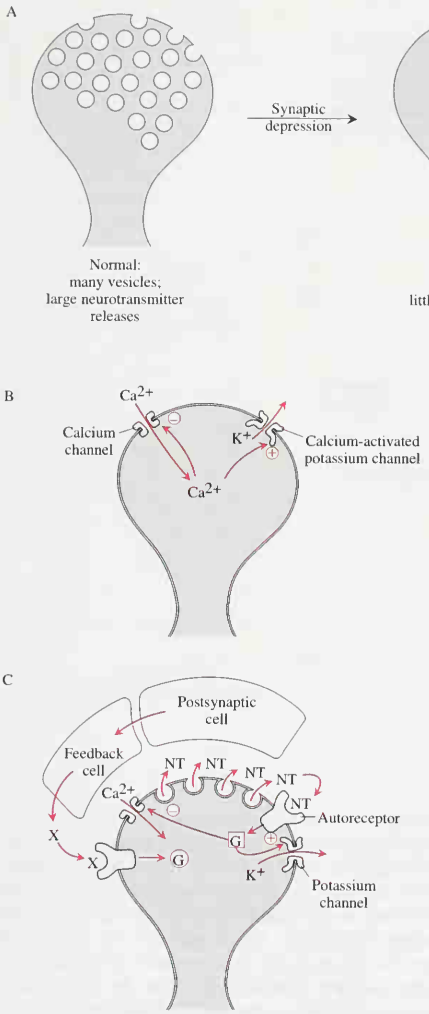


Figure 21.4
Three mechanisms for synaptic depression. (A) After repetitive presynaptic action potentials, the pool of releasable synaptic vesicles can be depleted, leaving fewer vesicles available to respond to subsequent action potentials. (B) Accumulation of calcium ions inside the terminal can inactivate calcium channels (−) or activate calcium-sensitive potassium channels (+). (C) The neurotransmitter molecules (NT) released by a synaptic terminal bind to autoreceptors on the surface of the terminal. The activated autoreceptors then activate G-proteins, leading to closure of voltage-dependent calcium channels (−) or opening of potassium channels (+). In addition, the postsynaptic cell contacted by the synaptic terminal can feed back either directly or indirectly and release a different neurotransmitter (X), which can also alter calcium- and/or potassium-channel opening.

rapid repolarization after an action potential. This also reduces calcium entry during an action potential and decreases neurotransmitter release.

Feedback mechanisms are also thought to play a role in synaptic depression (see Fig. 21.4C). In this type of scheme, the neurotransmitter released by previous action potentials feeds back, either directly or indirectly, onto the releasing terminal and influences the release of transmitter by subsequent action potentials. Indirect feedback can occur via presynaptic inhibition (see chapter 8). Direct feedback occurs via **autoreceptors** in the plasma membrane of the presynaptic terminal. Autoreceptors are activated by neurotransmitter released from the same synaptic terminal on which they are located. Because they are usually localized to parts of the synaptic terminal at a distance from the synaptic cleft (see Fig. 21.4C), these receptors are activated only when enough neurotransmitter is released to spill out of the synaptic cleft and reach the surrounding parts of the extracellular space. Autoreceptors are usually members of the G-protein–coupled family of receptors, linked indirectly to ion channels via intracellular second messengers. In some cases, the activated autoreceptors inhibit neurotransmitter release by closing calcium channels, which reduces the amount of calcium entering during a presynaptic action potential. In other cases, they are linked to the opening of potassium channels, which hyperpolarizes the terminal and speeds repolarization during a presynaptic action potential.

LONG-TERM CHANGES IN SYNAPTIC STRENGTH

Long-term potentiation

Short-term changes in synaptic strength produce activity-dependent increases or decreases in presynaptic neurotransmitter release on a time scale of seconds to minutes after a burst of activity. In addition, neuronal activity can lead to longer-term aftereffects that alter neurotransmitter release on a time scale of hours or days. Such long-lasting changes require different sorts of cellular mechanisms than those described above for short-term synaptic enhancement and depression. In this section, we will examine a particularly well-studied example of these long-term changes: **long-term potentiation (LTP).** As the name implies, LTP involves a long-lasting enhancement of synaptic strength. Although LTP occurs at a variety of sites within the nervous system, we will concentrate on LTP in synaptic connections within a brain region called the **hippocampus.**

We choose the hippocampus for our discussion because behavioral evidence suggests that this brain structure is involved in the formation of new memories—a finding that has motivated neurobiologists to focus a great deal of experimental attention on synaptic plasticity in the hippocampus. If the hippocampus is destroyed surgically or by disease, short-term memory (memory lasting a few seconds—like the memory we use to recall a phone number we have just looked up while we dial it) is unimpaired. Likewise, long-term memory (memory lasting years) of events that occurred before the destruction of the hippocampus remains unaffected. The ability to place new information into long-term memory is severely impaired, however, suggesting that the hippocampus is associated with a form of intermediate-term memory used to transfer information from short-term to long-term storage. The process by which this transfer takes place remains obscure.

Synaptic organization of the hippocampus

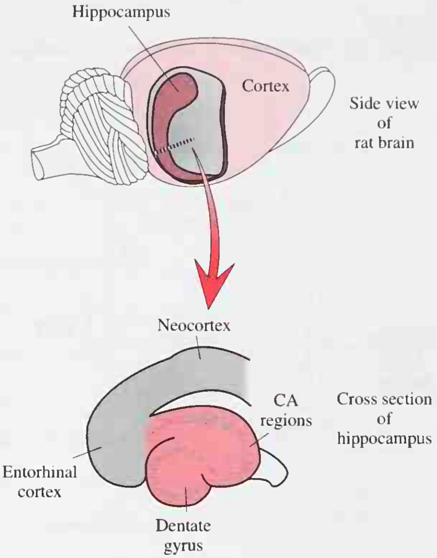
The location of the hippocampus is illustrated in Figure 21.5. The hippocampus is a tapered, C-shaped structure tucked under the lower lip of the neocortex. It is a form of cortex, like the neocortex, but the layering scheme is simpler. The hippocampus is also phylogenetically more ancient than neocortex, and thus is called **archicortex.** The two major parts of the hippocampus are the **dentate gyrus** and the **CA fields** (CA is an abbreviation for "cornu Ammonis," or "Ammon's horn"). The neurons of the CA fields are pyramidal neurons, shaped like the pyramidal neurons of neocortical areas discussed in previous chapters, and their cell bodies form a single layer. The neurons in the dentate gyrus also form a single layer, but they have rounded cell bodies and are called **granule cells.**

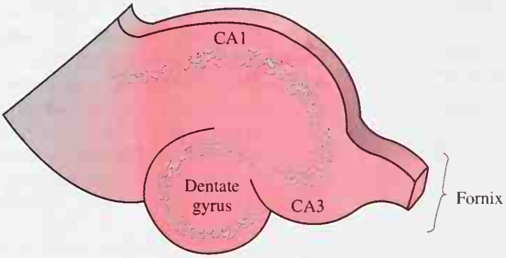
The synaptic connections within the hippocampus related to LTP are shown in Figure 21.6. Incoming axons from neurons in the **entorhinal cortex** enter the hippocampus via a fiber tract, the **perforant path**, and make excitatory synapses onto granule cells in the dentate gyrus. The granule cells in turn send axons (**mossy fibers**) to **subregion CA3** of the CA fields, where they make excitatory synapses onto pyramidal cells. The CA3 pyramidal cells send axons out of the hippocampus via the **fornix**, a large fiber bundle connecting the hippocampus to other brain regions (including the contralateral hippocampus). In addition, the axons of the CA3 cells branch and make excitatory connections with pyramidal cells of **region CA1** of the CA fields. The axon branches of the CA3 neurons extending to region CA1 are called **Schaffer collaterals**. All of the excitatory synapses within the hippocampus release the neurotransmitter glutamate, an important point to keep in mind when we discuss proposed mechanisms of long-term potentiation.

Long-term potentiation is associative

All three excitatory synaptic pathways within the hippocampus show post-tetanic potentiation. That is, a burst of high-frequency activity in the presynaptic axons enhances subsequent postsynaptic excitatory responses. Instead of lasting minutes, however, the enhanced postsynaptic response persists for as long as one week or more. This facet of the process makes long-term potentiation interesting as an event that produces enduring changes in synaptic effectiveness. Another property of LTP inspires even more interest: the potentiation is *heterosynaptic* and *associative*. This is illustrated in Figure 21.7. Not only is synaptic transmission enhanced after strong stimulation in the synapses that received the strong stimulation, but it is also enhanced in synapses that were only weakly stimulated, as long as the weak stimulation was closely temporally associated with the strong stimulus. In other words,

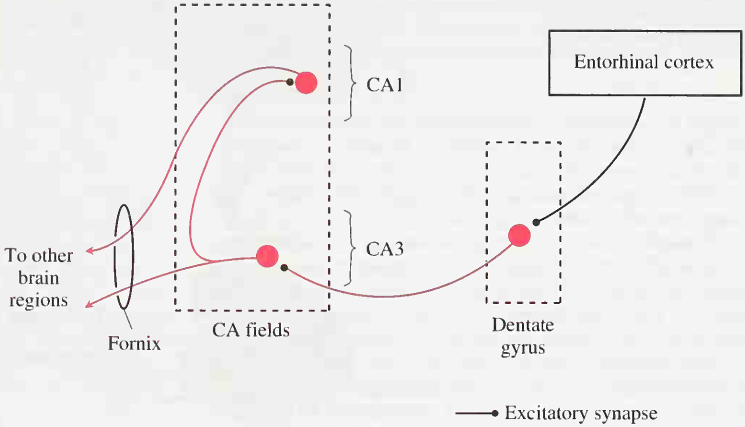
Figure 21.5
The location of the hippocampus in the rat brain. The upper drawing shows the overall location of the hippocampus. The lower drawing shows a cross section in the plane indicated in the upper drawing.





weakly stimulated synapses that are active contemporaneously with strong stimulation of the postsynaptic cell become potentiated. Furthermore, the potentiation does not produce a general increase of all synaptic inputs by strong stimulation, regardless of whether the synapses were silent or active during the strong stimulus. Instead, the weakly active synapses must be activated (albeit weakly) nearly simultaneously with the strongly activated synapses to initiate the potentiation, and synapses that are silent during the strong stimulation are not potentiated (see Fig. 21.7).

Figure 21.6
The excitatory synaptic circuitry within the hippocampus.



The strengthening of one set of synapses by association with activity in another set of synapses is similar to associative learning in some ways. In **classical** or **Pavlovian conditioning**, a neutral stimulus (the **conditioned stimulus**, or CS) is paired temporally with a salient stimulus that evokes a biological response (the **unconditioned stimulus**, or UCS). The CS then acquires the ability to elicit the biological response evoked by the UCS. The classic example is a dog salivating in response to a bell that was previously paired with the presentation of food. Although there is no evidence that LTP actually underlies such a learning process, it is intriguing that the required temporal relationship is also observed in LTP and that the changes in synaptic strength persist for long periods in a part of the brain known to be involved in memory.

Mechanism of long-term potentiation

Much progress has been made toward a molecular understanding of how LTP arises, and large parts of the picture have become clear. It is not yet possible, however, to specify unequivocally the mechanisms involved in LTP. In this section, we will examine some reasonable models of LTP that incorporate the key features of the phenomenon.

First, what aspect of strong stimulation triggers synaptic strengthening in the strongly stimulated synapses and in coactive, weakly stimulated synapses? The answer is quite simple: strong synaptic stimulation produces substantial depolarization of the postsynaptic neuron, and *depolarization of the postsynaptic neuron initiates LTP* (Fig. 21.8). Even when tetanic stimulation

Figure 21.7
Long-term potentiation of excitatory synapses in the hippocampus. (A) A schematic diagram of a pyramidal neuron in subregion CA1, receiving excitatory synapses from three Schaffer collateral axons. The axons are labeled 1, 2, and 3, and each one can be separately stimulated to fire an action potential. (B) Prior to potentiation, each input synapse produces a similar excitatory postsynaptic potential (black traces labeled "post"). Each of the three inputs (numbered 1–3 on the left of the traces) is stimulated separately to fire a single presynaptic action potential (red traces labeled "pre"). (C) A rapid burst of action potentials is triggered in input 1, while input 2 fires at a low rate and input 3 remains inactive. Although postsynaptic traces are not shown for simplicity, the burst of action potentials in input 1 would produce summated e.p.s.p.'s and substantial depolarization of the postsynaptic cell. (D) One hour after the potentiating burst of action potentials, the postsynaptic responses to single action potentials in the three input fibers are tested. The e.p.s.p.'s elicited by input 1 and by input 2 are larger, while the response to input 3 remains the same as before potentiation.

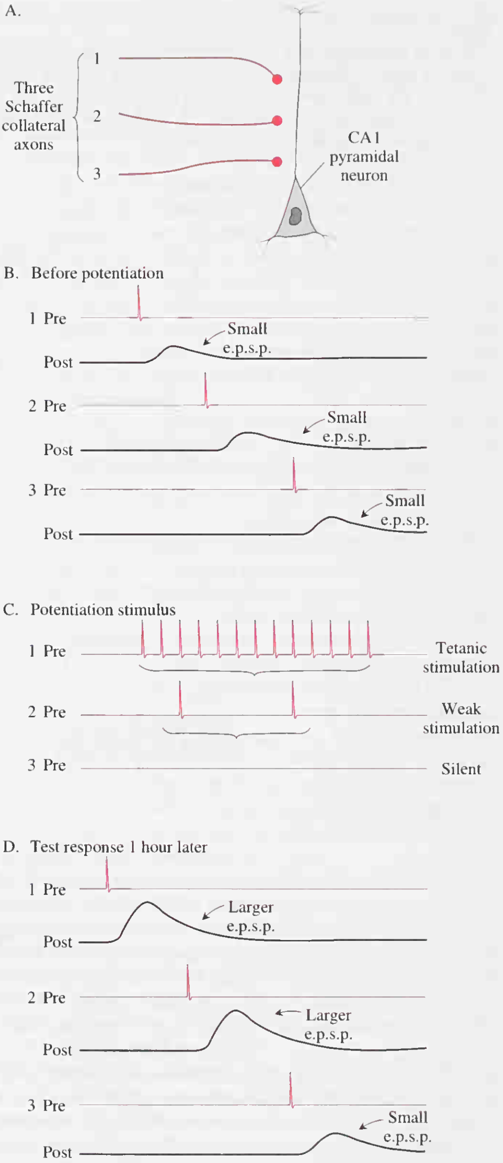
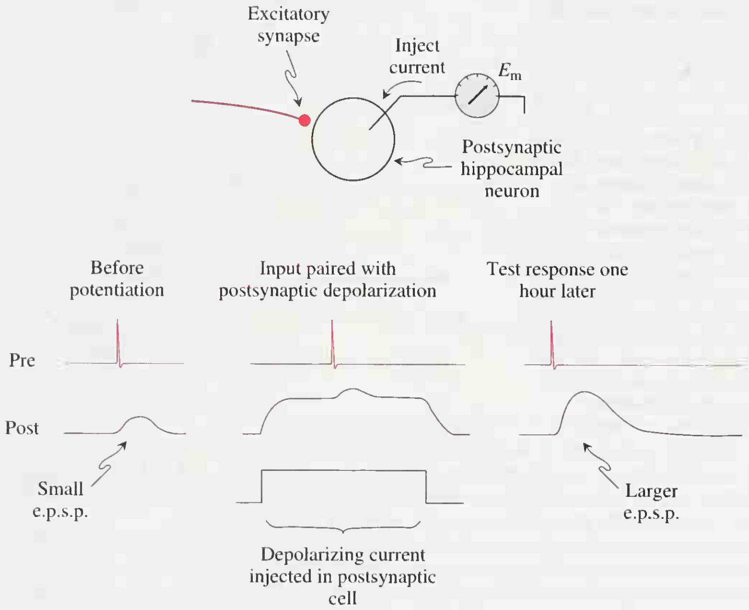


Figure 21.8
Long-term potentiation in a single input can be triggered by postsynaptic depolarization. A single excitatory input is stimulated to fire a single action potential (red traces labeled "pre"). Before potentiation, the postsynaptic response is a small e.p.s.p. After the stimulation of the input is paired with depolarizing current injected into the postsynaptic cell (middle set of traces), the postsynaptic response is enhanced (right set of traces).


Excitatory synapse
Inject current
E_m
Postsynaptic hippocampal neuron
Before potentiation
Input paired with postsynaptic depolarization
Test response one hour later
Pre
Post
Small e.p.s.p.
Larger e.p.s.p.
Depolarizing current injected in postsynaptic cell

of the presynaptic inputs is missing, LTP can be triggered if activity in presynaptic cells is paired with depolarization of the postsynaptic cell produced artificially by injecting depolarizing current. Under normal circumstances, the necessary amount of postsynaptic depolarization occurs only when multiple synaptic inputs are repetitively stimulated, so that the combined spatial and temporal summation of the resulting excitatory postsynaptic potentials strongly depolarizes the postsynaptic neuron. This requirement for strong postsynaptic depolarization explains why tetanic stimulation of the input fibers is normally required to elicit LTP.

How does depolarization of the postsynaptic cell affect subsequent synaptic responses, and why does the potentiation affect only those synapses that are active during the depolarization? To answer these questions, we must first examine the anatomical arrangement of the excitatory synapses in the hippocampus and the properties of the postsynaptic receptor molecules that detect glutamate release by the presynaptic terminals. As with many other excitatory synapses in the central nervous system, the synaptic terminals contact the dendrites of hippocampal neurons at short, hair-like protuberances called **dendritic spines.** At high magnification, each spine is seen to consist of a knob-like swelling connected via a thin neck of cytoplasm to the main branch of the dendrite, as shown schematically in Figure 21.9. The thinness of the connecting neck allows each spine to behave as a separate intracellular compartment, within which biochemical events can occur in isolation from the rest of the cell. Thus, internal signals can be generated in one spine without spreading to and affecting other spines on the dendrite. Each spine receives input from a single excitatory synaptic terminal. The combination of one terminal and one spine therefore creates a functional synaptic unit that can be modulated separately from the other units on the dendrite of a single neuron. This structural organization may have important ramifications for the selectivity of potentiation for active synapses, in that it leaves inactive synapses unpotentiated.

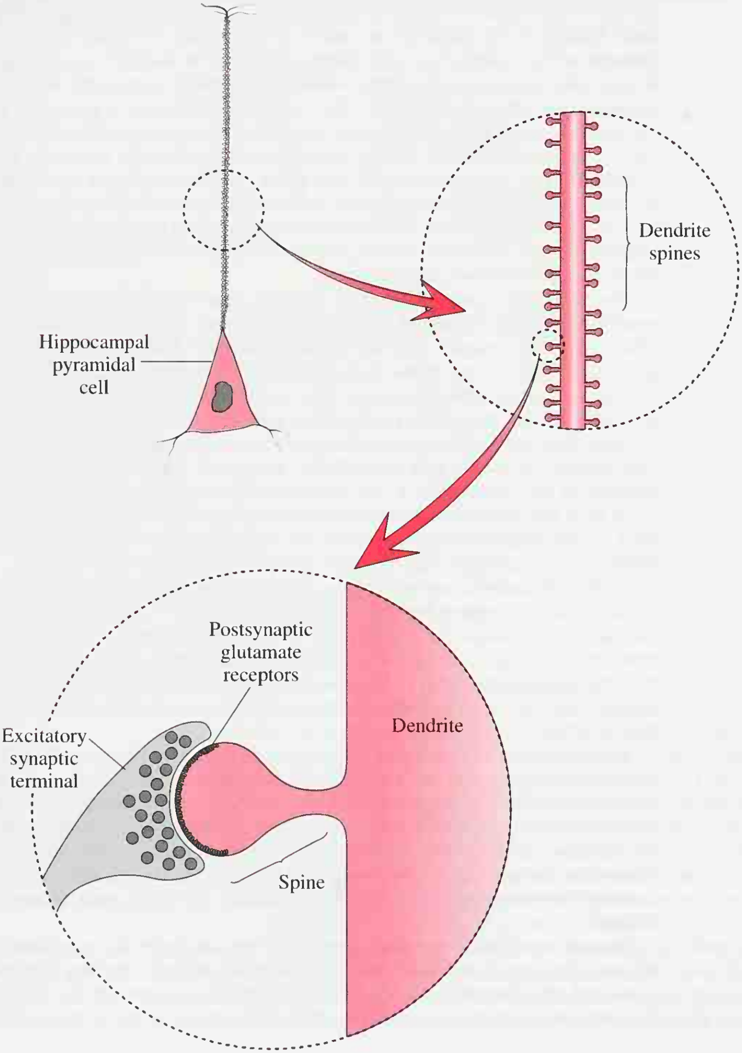
The excitatory neurotransmitter released from the synaptic terminals onto the dendritic spines of hippocampal neurons is glutamate. As with other excitatory synapses (see, for example, chapters 7 and 8), the released glutamate binds to and opens ligand-gated ion channels (glutamate receptors) in the postsynaptic membrane. This process changes ionic permeability and leads to the excitatory postsynaptic potential (e.p.s.p.). At glutamate synapses that show LTP, there are two types of postsynaptic glutamate receptors: **NMDA receptors** and **non-NMDA receptors.** Both types are mixed together in the membrane of the dendritic spine just opposite the contact point with the presynaptic terminal. This situation differs from that encountered at the neuromuscular junction, for example, where all postsynaptic receptors are of a single type (nicotinic acetylcholine receptors).

NMDA (N-methyl-D-aspartate) is an artificial glutamate analogue that can activate NMDA receptors but not non-NMDA receptors. This pharmacological difference between the two receptor types is not important for LTP; both types are activated by glutamate released into the synaptic cleft by presynaptic action potentials. However, there are two important functional differences between NMDA and non-NMDA receptors that are important for the generation of LTP.

First, although both receptor types are nonspecific cation channels, non-NMDA receptors do not have appreciable permeability for calcium ions. In contrast, NMDA receptors permit influx of calcium ions when the channel is open. Thus, the non-NMDA receptors increase the postsynaptic permeability to potassium and sodium ions, like the nicotinic acetylcholine-activated channels at the neuromuscular junction (see chapter 7). The NMDA receptors increase the postsynaptic permeability to calcium, as well as potassium and sodium.

Second, non-NMDA receptors open when glutamate binds, regardless of the membrane potential, but NMDA receptors require both binding of glutamate and depolarization to open. The voltage-dependence of the NMDA receptors does not arise from an inherent voltage sensor in the channel, as is

Figure 21.9
Excitatory synapses onto hippocampal pyramidal cells are made onto spike-like protrusions of the dendrites, called dendritic spines.


Dendrite spines
Hippocampal pyramidal cell
Postsynaptic glutamate receptors
Excitatory synaptic terminal
Dendrite
Spine

the case for the voltage-dependent sodium and potassium channels that underlie the action potential (see chapters 5 and 6). Instead, the NMDA receptors fail to conduct inward current in the presence of glutamate at negative membrane potentials because external magnesium ions block the channels. Magnesium, a divalent cation, enters the channel down the electrical gradient across the membrane when the membrane potential is strongly negative. Unlike calcium, however, it does not move through the open NMDA channel, but plugs up the pore. Upon depolarization, the electrical gradient is reduced, and magnesium becomes less likely to enter and block the open channel.

The behavior of the NMDA and non-NMDA glutamate receptors is summarized in Figure 21.10. In the absence of strong excitatory synaptic activity, the postsynaptic membrane potential remains at its usual negative level. Under these conditions, glutamate released from a single presynaptic terminal opens non-NMDA receptors on its corresponding spine; it does not open the NMDA receptors because they require both glutamate and depolarization. Thus, the postsynaptic permeability to sodium and potassium increases, and a small e.p.s.p. will arise that is governed by the non-NMDA receptors acting alone. A single action potential in a single presynaptic terminal produces only a small postsynaptic depolarization, which is insufficient to depolarize the postsynaptic neuron into the range of membrane potential required to open the NMDA channels.

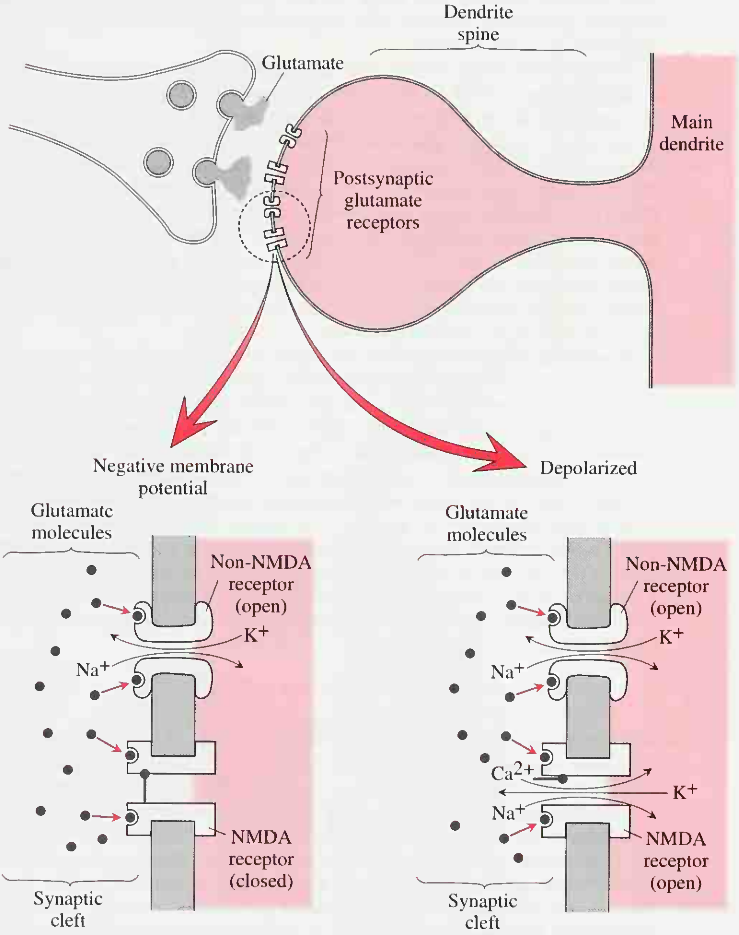
If multiple synaptic terminals are active simultaneously, the summated e.p.s.p.'s depolarize the postsynaptic cell to a greater extent. With this greater depolarization, both the NMDA and non-NMDA receptors open when glutamate is released from the presynaptic terminal. *The open NMDA receptor channels allow calcium influx, which is the actual trigger for LTP.* Because each spine is separated from its neighbors, the internal calcium concentration increases only in the spines whose terminals are releasing glutamate at the time of depolarization. The synapse at a neighboring spine whose terminal is not active will not become potentiated because no glutamate is available there to occupy NMDA receptors. Thus, synaptic inputs that are active during a period of depolarization (which would normally correspond to a period of intense excitatory synaptic activity) will become potentiated, while silent inputs will not.

Long-term potentiation may involve presynaptic and postsynaptic changes

How does the increase in internal calcium in the dendritic spine cause long-term potentiation of the synapse? Here the picture becomes a bit fuzzy, despite intense research activity in recent years. The size of an e.p.s.p. can be increased in two ways: by increasing the amount of neurotransmitter released by a presynaptic action potential (presynaptic mechanisms) or by increasing the postsynaptic sensitivity to a fixed amount of released neurotransmitter (postsynaptic mechanisms). We have already seen several instances in which the amount of neurotransmitter released per action potential can be increased (see, for example, our discussion of short-term synaptic enhancement earlier in this chapter). An example of a postsynaptic mechanism might

Figure 21.10

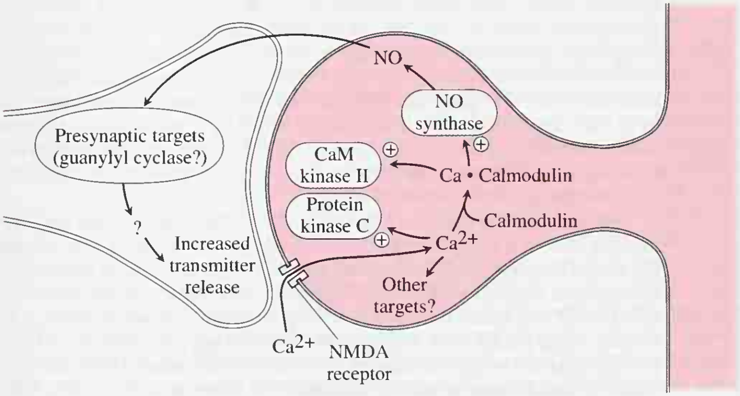
The postsynaptic membrane of the dendritic spine contains two types of glutamate receptors: NMDA receptors and non-NMDA receptors. Both require binding of the neurotransmitter glutamate to open (bottom diagrams); NMDA receptors also require depolarization of the postsynaptic cell in order to open. Both glutamate receptor types allow sodium and potassium ions to move through the open channel, but the NMDA receptor also admits calcium ions.



include an increase in the density of functional glutamate receptors in the postsynaptic membrane of the dendritic spine. Evidence suggests that both presynaptic and postsynaptic factors can contribute to long-term potentiation in the hippocampus, although there is disagreement about the relative importance of these processes.

If LTP is, at least in part, attributable to an increase in neurotransmitter release, then the question immediately arises of how an increase in calcium in the *postsynaptic* cell triggers a change in the release characteristics in the *presynaptic* cell. Clearly, a signal must be transmitted back from the dendritic spine to the synaptic terminal—that is, a **retrograde signal** must be issued. Although the identity of this retrograde signal remains unknown, one proposed signaling scheme is illustrated in Figure 21.11. Among the cellular targets for elevated calcium in the dendritic spine is **nitric oxide synthase**, which is an enzyme that produces **nitric oxide** (chemical structure = NO) from the amino acid arginine. The released NO is a small, membrane-permeant molecule that can readily diffuse from the dendritic spine into the presynaptic terminal. NO is also known to act as a cellular messenger in other body tissues and can activate intracellular signaling molecules, including guanylyl cyclase. In this scheme, therefore, elevated calcium levels in the postsynaptic cell activate NO synthase. The released NO diffuses into the

Figure 21.11
Nitric oxide (NO) may be a retrograde messenger at hippocampal synapses. Calcium influx through NMDA receptors increases intracellular calcium, which binds to calmodulin. Calcium/calmodulin then activates two enzymes: nitric oxide synthase (NO synthase) and calcium/calmodulin-dependent protein kinase II (CaM kinase II). Calcium also activates protein kinase C. NO synthase produces NO from arginine, and the membrane-permeant messenger is thought to diffuse to the presynaptic terminal. It then interacts with cellular signaling pathways, possibly including guanylyl cyclase, to potentiate transmitter release.



presynaptic terminal, where it activates an unknown biochemical cascade leading to enhanced neurotransmitter release.

Calcium within the dendritic spine also has other cellular targets (see Fig. 21.11), including factors that could produce an increased postsynaptic sensitivity to released glutamate, which has been suggested to underlie LTP. Two types of kinase are activated by elevated calcium: **protein kinase C (PKC)** and **calcium/calmodulin-dependent kinase II (CaM kinase II)**. When activated by elevated calcium, these enzymes phosphorylate specific target proteins in the postsynaptic cell. As we saw with neuronal growth factors in chapter 20, phosphorylation is a cellular signal often used to activate or inactivate various kinds of proteins. In the case of LTP, however, the mechanism by which kinase activation increases the size of e.p.s.p.'s has not been established. Some researchers speculate that phosphorylation increases the number of functional postsynaptic glutamate receptors, either because phosphorylation allows the channels to open in response to glutamate or because phosphorylation tethers channels to the cytoskeleton, thereby anchoring them at the appropriate position in the postsynaptic membrane.

LTP can likely be produced in the nervous system by processes other than the mechanism described here involving postsynaptic NMDA receptors. Even within the hippocampus, LTP can arise in several ways. For example, LTP can be readily induced at the synaptic connection between granule cells of the dentate gyrus and the pyramidal cells of area CA3 (see Fig. 21.6). At this synapse, however, the postsynaptic response to glutamate does not involve NMDA receptors. Thus, alternative ways to initiate LTP must exist, besides the depolarization-dependent influx of calcium through NMDA receptors (see Fig. 21.10). Because synaptic plasticity plays such an important role in the alteration of behavior based on experience, it should not be surprising that multiple mechanisms have evolved to accomplish this task.

Long-term depression of synaptic strength

In our discussion of short-term changes in synaptic strength, we saw that synaptic efficacy can either decrease or increase as a result of presynaptic activity. The same is true for longer-term changes in synaptic strength. **Long-term depression (LTD)**, lasting hours or weeks, is also observed at synaptic connections in a variety of brain regions. The stimulation conditions that elicit LTD differ somewhat at various synapses. In some cases, such as in the cerebellum, LTD is associative—that is, it requires the temporal pairing of two different synaptic inputs. In other cases, LTD is homosynaptic—that is, it is based on activity in one set of synapses without requiring coactivation of a different set of synapses.

Interestingly, the excitatory synapses within the hippocampus also demonstrate LTD. If a synaptic input is activated at a low rate for a few minutes, the size of the e.p.s.p. elicited by that synaptic input diminishes and remains at this lower level for many hours. In a sense, this scenario is the opposite of LTP. In LTP, the effectiveness of a weakly stimulated synaptic input is enhanced when paired with strong activation of other pathways. In LTD, the effectiveness of a weakly stimulated synapse becomes reduced if its activation occurs in the absence of strong stimulation in other synaptic inputs. If LTP is induced for a particular synapse, it can subsequently be reversed by LTD. This relationship suggests that LTD represents an erasure mechanism for LTP in the hippocampus: unless activation of a synaptic input is *consistently* strongly activated or paired with strong activation of the postsynaptic cell, the potentiation of that input is reversed by the development of LTD.

Even less is known about the mechanism of LTD in the hippocampus than the mechanism of LTP. Evidence suggests that LTD may involve the activation of protein phosphatases, enzymes that remove the phosphate groups from previously phosphorylated proteins. Given that phosphorylation has been proposed as a mediator of at least some aspects of LTP, the activation of dephosphorylating enzymes would appear to be an attractive mechanism for reversing potentiation.

MODIFICATION OF SYNAPTIC STRENGTH IN REFLEX CIRCUITS

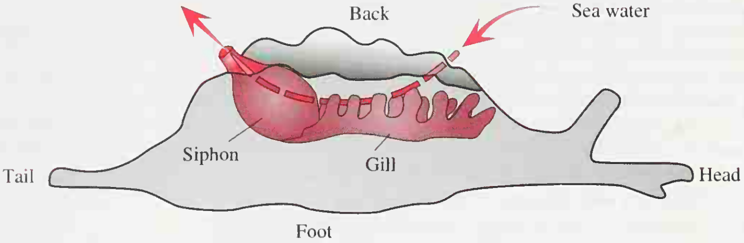
We have frequently used reflexes of various kinds as examples when learning about neuronal signals and their interactions. The simplicity of these reflex circuits allows us to readily appreciate the underlying principles of circuit organization. Even these simple neuronal circuits are capable of modification based on experience, however. In this section, we will consider some examples of reflexive learning; in each case, we will try to take our description to a molecular level as much as is permitted by the current state of knowledge. In these examples, we will see that learning is accompanied by changes in the effectiveness of synaptic connections that are quite similar to the changes we encountered when considering short-term alterations in synaptic efficacy.

Habituation

Our first example of simple learning in a reflex circuit is reflex habituation. If a stimulus is presented repeatedly, it typically becomes increasingly less effective in eliciting a reflexive response. This reduction of response strength with repetition of a stimulus is called **habituation.** It allows the nervous system to disregard constant stimuli and accentuate changing conditions. The best-studied example of habituation of a reflex is a type of withdrawal reflex in the sea slug, *Aplysia californica.* Like other gastropod molluscs, *Aplysia* has a relatively simple nervous system and a correspondingly simple repertoire of behaviors. This facilitates the task of sorting out the neural circuitry responsible for particular aspects of behavior and thus makes it feasible to discern the changes in circuitry that underlie behavioral changes.

The overall body structure of *Aplysia* is shown in Figure 21.12. The animal's respiratory organ, the gill, resides within a fleshy pouch on the dorsal surface. Under normal circumstances, the lips of the pouch remain slightly open to allow entry of sea water, which is expelled toward the rear of the animal through a spout called the siphon. In this way, a steady flow of water moves over the gill. If the extended siphon is touched, the siphon

Figure 21.12
The sea slug, *Aplysia californica*. When the siphon is touched, the siphon and gill are reflexively retracted within a protective pocket on the animal's back.



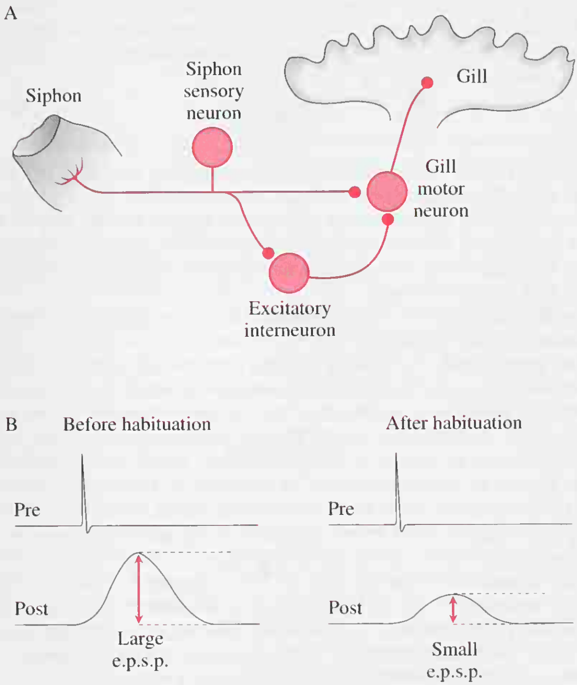
and gill are reflexively withdrawn into the pouch, and the pouch closes. This defensive reflex protects the more vulnerable, fleshy parts of the animal from predators. With time, the withdrawn body parts resume their normal positions. If another tactile stimulus is then applied to the siphon, withdrawal occurs more slowly and is less complete. After a series of touch stimuli, the reflex habituates, and the gill no longer withdraws when the siphon is touched. Similarly, if a tactile stimulus is applied to the tail of the animal, the tail contracts and withdraws; this withdrawal reflex also habituates with repeated tactile stimulation.

What neuronal changes produce habituation of the withdrawal reflex? The circuitry of the gill withdrawal reflex is shown in Figure 21.13A. Touch-sensitive sensory neurons make excitatory synapses directly onto motor neurons that control the gill muscles. In addition, the sensory neurons make excitatory synapses with interneurons, which then make excitatory connections with the gill motor neurons. Thus, there are both direct and indirect synaptic paths from the sensory neurons to the gill motor neurons.

In the unhabituated state, each action potential in a sensory neuron produces a large e.p.s.p. in the motor neurons (Fig. 21.13B) and the interneurons. The interneurons also produce a strong e.p.s.p. in the motor neurons. Through these direct and indirect synaptic connections, a burst of action potentials in the touch-sensitive sensory neuron produces a prolonged, high-frequency discharge in the motor neurons and a rapid, complete withdrawal of the gill.

If the tactile stimulus is repeatedly presented, producing habituation of the reflex, the e.p.s.p.'s produced by the sensory neurons in the motor neurons and in the interneurons become progressively smaller, as shown in Figure 21.13B. In addition, the synaptic connection between the interneurons and the motor neurons also becomes weaker. The overall result is that fewer action potentials are evoked in the gill motor neurons in response to touch of the siphon, and so the strength of the reflexive withdrawal declines. Thus, habituation of the withdrawal reflex is produced by synaptic

Figure 21.13
The neural circuit for the gill withdrawal reflex in *Aplysia*. (A) Touch-sensitive sensory neurons that innervate the siphon project both directly and indirectly via interneurons to the motor neurons of the gill muscles. (B) Habituation of the withdrawal reflex is produced by synaptic depression in the excitatory synapses of the neural circuit.



depression in the excitatory synapses of the underlying neuronal circuit. The mechanism of the depression is thought to involve inactivation of calcium channels in the presynaptic terminals and reduction in the pool of synaptic vesicles available for release at each synaptic active zone. Both of these mechanisms are among those we described earlier in this chapter in our discussion of short-term synaptic depression.

Sensitization

A reflex may not only be weakened on the basis of experience, but it can also be strengthened. For example, exposure to a painful or noxious stimulus produces a generalized increase in the vigor of withdrawal reflexes, a phenomenon called **sensitization.** The presence of a noxious stimulus may signify that the organism has entered a hostile environment, and therefore the potentiation of defensive withdrawal reflexes is adaptive. The sensitizing stimulus can lie outside the sensory realm of the reflexes that are potentiated. For instance, a pinch applied to an animal's tail potentiates withdrawal reflexes of the foot. This situation differs from habituation, in which the stimulus that elicits the reflex is itself the stimulus that leads to the change in reflex strength. Therefore, we would expect the synaptic mechanisms of sensitization to differ from those of habituation. As we will see, this is indeed the case.

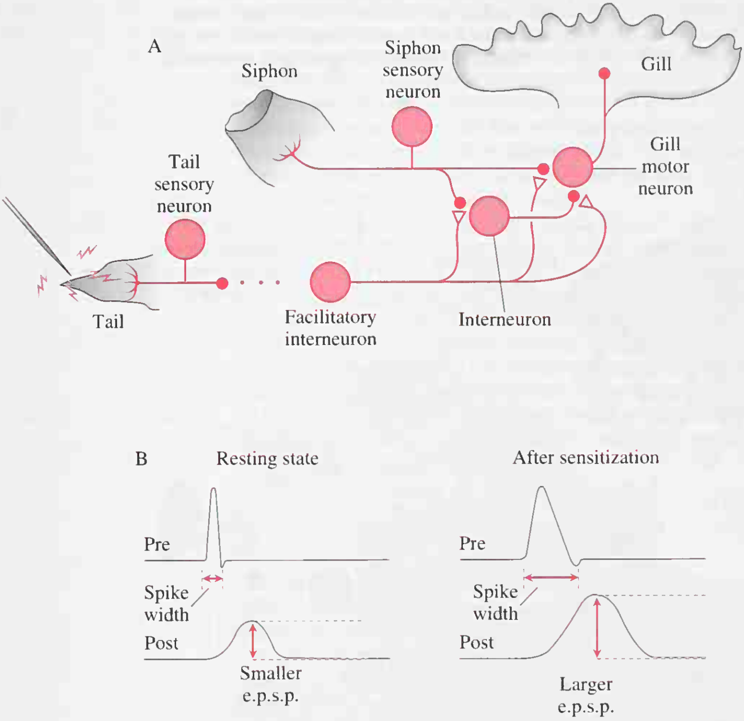
Facilitation of neurotransmitter release underlies sensitization

To examine the cellular mechanisms of sensitization, we return to the gill withdrawal reflex of *Aplysia*. If an electrical shock (which a human would perceive as painful) is applied to the tail of the animal and its siphon is touched at a later time, the withdrawal of the gill is more rapid and vigorous than usual. In other words, the gill withdrawal reflex exhibits sensitization in response to a noxious stimulus.

To account for sensitization, we must expand the circuit for the withdrawal reflex to include inputs originating from the sensory neurons of the tail. This is shown in Figure 21.14A. The sensory neurons from the tail indirectly excite a class of interneurons, called **facilitatory interneurons,** which make synaptic contact with the presynaptic terminals of the excitatory synapses in the gill withdrawal circuit. Activation of the facilitatory interneurons does not produce a typical i.p.s.p. or e.p.s.p. in the postsynaptic target, but instead enhances the release of neurotransmitter in response to presynaptic action potentials of the synapses of the withdrawal circuit. Upon stimulation of the facilitatory interneurons, each action potential in the sensory neuron produces a larger-than-normal e.p.s.p. in its postsynaptic target neurons (the motor neurons and interneurons) (Fig. 21.14B). The same is true for the excitatory synapses from the interneurons onto the motor neurons. This process produces greater excitation of the motor neurons and a stronger reflex response. Thus, the enhancement of the postsynaptic response reflects increased release of neurotransmitter from the presynaptic terminal.

Figure 21.14B illustrates another important effect produced by the facilitatory interneuron: the duration of the presynaptic action potential *increases*. This immediately suggests a mechanism for the enhanced release of neurotransmitter. Recall from chapters 5 and 6 that the potassium permeability of the membrane is an important factor in the repolarization phase of action potentials. A slowing of repolarization implies a reduced potassium permeability. This mechanism applies to the action of the facilitatory interneuron on the synaptic terminals in the gill withdrawal circuit. Figure 21.15 summarizes the mechanism currently thought to produce this effect. The facilitatory interneurons release the neurotransmitter serotonin (other neurotransmitters are probably used by some interneurons, but we will focus on serotonin). Serotonin binds to and activates receptors in the membrane of the presynap-

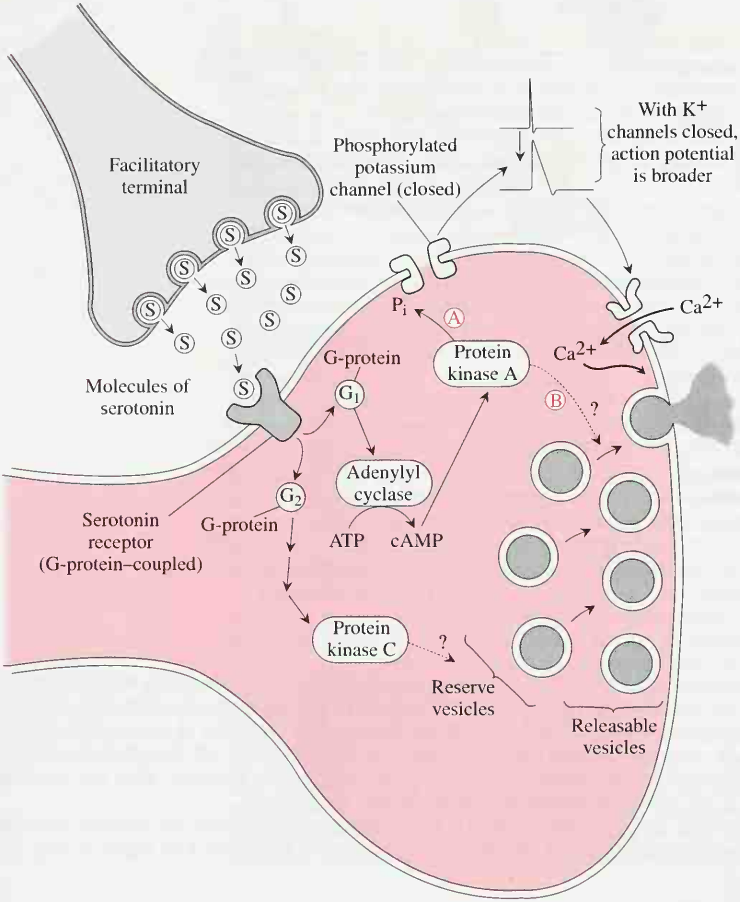
Figure 21.14
The neural basis of sensitization of the gill withdrawal reflex in *Aplysia*. (A) The excitatory synapses in the gill withdrawal circuit receive presynaptic inputs from a facilitatory interneuron. The facilitatory interneuron is activated by noxious stimuli applied to the tail of the animal. (B) Sensitization produces larger excitatory postsynaptic potentials in the withdrawal circuit, reflecting the longer duration of the presynaptic action potential after sensitization.



tic terminals of the siphon sensory neuron. These receptors then activate one or more types of G-proteins inside the synaptic terminal. One type of G-protein stimulated by serotonin binding is an activator of the enzyme adenylyl cyclase, which produces cyclic AMP (cAMP) from ATP, thereby increasing the concentration of cAMP inside the synaptic terminal. This rise in cAMP enhances neurotransmitter release in two ways.

First, the increased cAMP enhances the influx of calcium ions into the terminal during an action potential (pathway A in Figure 21.15). This

Figure 21.15
A model for presynaptic changes associated with sensitization of the gill withdrawal reflex in *Aplysia*. The synaptic terminals of the facilitatory interneuron release the neurotransmitter serotonin, which combines with serotonin receptors in the membrane of the excitatory synaptic terminals of the gill withdrawal circuit. The activated receptor stimulates two G-proteins: one increases intracellular cyclic AMP via adenylyl cyclase, and a second activates protein kinase C. Cyclic AMP stimulates protein kinase A, which in turn phosphorylates and closes potassium channels. This process broadens the presynaptic action potential and enhances calcium influx through voltage-dependent calcium channels. In addition, protein kinase A and possibly protein kinase C may promote movement of synaptic vesicles from reserve pools to releasable pools, thereby potentiating transmitter release.



increased calcium flow is probably a direct result of the longer duration of the presynaptic action potential. The effect of cAMP on the action potential is mediated by protein kinase A (the cAMP-stimulated protein kinase). In this case, the target protein phosphorylated by the activated kinase is a type of potassium channel, which does not open when it is phosphorylated. The inhibition of these potassium channels slows repolarization after an action potential, causing voltage-activated calcium channels to remain open for longer periods. Thus, a single action potential releases a greater amount of neurotransmitter.

Second, the number of synaptic vesicles available to be released by a presynaptic action potential may increase in response to cAMP. This effect may be generated by the movement of vesicles from a reserve group onto the active zones, where they can fuse with the plasma membrane in response to calcium influx (pathway B in Figure 21.15). The evidence for this second effect of cAMP on releasable vesicles is not yet firm, and this aspect of the model should be regarded as speculative.

Some evidence indicates that protein kinase C (PKC) is also involved in enhancing neurotransmitter release during sensitization. This kinase has already been mentioned as possibly playing a role in long-term potentiation in the hippocampus. In the case of sensitization of the withdrawal reflex, serotonin receptors indirectly activate PKC via a pathway initiated by a different subclass of G-protein (see Fig. 21.15). The cellular targets for PKC are not well established as yet. Action potentials become broader when PKC is activated, which potentiates calcium influx as described above. The broadening of the action potential reflects closure of potassium channels, as in the case of protein kinase A. In addition, PKC may increase the pool of releasable synaptic vesicles at active zones.

The transition from short-term to long-term habituation and sensitization

The cellular mechanisms described above produce habituation and sensitization of the gill withdrawal reflex lasting a few minutes. If we expose an animal to repetitive bouts of habituation or sensitization, however, we can produce changes in the strength of the reflex lasting for days or weeks. What factors account for the transition from short-term to long-term changes in reflex excitability after repetitive experience? Not all—or even very many—of the molecular answers to this question have been found. One hint is that RNA synthesis and protein synthesis are required for long-term sensitization of the gill withdrawal reflex. Short-term sensitization is unaffected by inhibition of RNA and protein synthesis, as expected from the fact that the scheme shown in Figure 21.15 for short-term sensitization depends on already-existing proteins within the synaptic terminal. The requirement for new RNA and new protein shifts the focus from the presynaptic terminal, where the short-term changes occur, to the cell body of the neuron, where RNA is transcribed and new protein molecules are synthesized. Thus, some signal appears to be sent from the synaptic terminal to the cell nucleus after repetitive bouts of sensitization, producing long-term changes in synaptic strength.

Long-term synaptic facilitation in the gill-withdrawal circuit can be triggered by elevated levels of intracellular cAMP, which is the cellular signal involved in at least part of short-term sensitization (see Fig. 21.15). This observation leads to the suggestion, as yet unproven, that cAMP-dependent gene transcription factors turn on genes involved in long-term facilitation of neurotransmitter release in the sensory neuron. Such cAMP-dependent transcription factors are known to exist in neurons and play important roles in other situations in the regulation of neuronal gene expression. The current theory is that protein kinase A, which is activated in the synaptic terminal during sensitization, finds its way to the cell body of the neuron, where it phosphorylates and activates transcription-factor proteins. The transcription factors then bind to the regulatory regions of the required genes and initiate the production of proteins necessary for maintaining the facilitated state of the synaptic terminals. These proteins have not yet been identified, although some may be transcription factors that in turn either activate or suppress other genes.

Some researchers hypothesize that this cascade of gene regulation ultimately reduces the amount of the regulatory subunit of protein kinase A. Like many other signaling proteins (for example, heterotrimeric G-proteins), protein kinase A consists of multiple protein subunits. Two different subunits make up protein kinase A: a **catalytic subunit**, which is the kinase enzyme that phosphorylates target proteins, and a **regulatory subunit**, which binds to and inhibits the catalytic subunit. (Actually, two copies of each subunit are found in a complete protein kinase molecule.) If the amount of regulatory subunit present in the cell is insufficient to bind all of the catalytic subunits, protein kinase A will be continually activated, even at basal levels of cyclic AMP. This would produce a persistently facilitated synapse. The amount of regulatory subunit is thought to be reduced by selective proteolysis, suggesting that genes encoding proteins that promote proteolysis are activated during long-term sensitization.

Although these changes in cAMP signaling may be partly responsible for long-term changes in synaptic efficacy, other mechanisms may also play a role. Anatomical experiments suggest that some long-term synaptic changes produced by repetitive habituation and repetitive sensitization reflect changes in the *number* of synaptic connections between the sensory neurons and the motor neurons in the reflex circuit. Correlated with the development of long-term sensitization, there is an increase in the number of synapses made by the sensory neuron on the motor neuron. A larger number of synaptic connections produces greater spatial summation of postsynaptic effects and thus larger excitatory postsynaptic potentials. Conversely, after long-term habituation, the number of synapses declines below normal levels. No changes in the number of synapses are observed during short-term habituation or sensitization. The synaptic connectivity pattern among neurons is plastic, not fixed. Evidence from imaging studies in the intact nervous system suggests that addition and subtraction of synaptic connections occurs on a continual basis in the nervous system. Thus, long-term changes in synaptic strength may act by biasing this ongoing process toward larger or smaller numbers of synaptic contacts, based on the recent history of neuronal activity in a circuit.

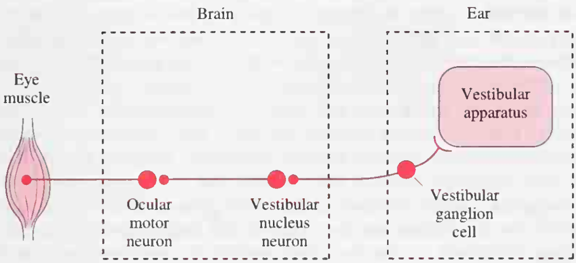
REFLEX PLASTICITY IN THE PRIMATE CENTRAL NERVOUS SYSTEM

Learning in the vestibulo-ocular reflex

Changes in reflex circuits based on experience are not restricted to marine molluscs, like *Aplysia*. Even in the primate brain (including that of humans), such reflexive learning occurs. A well-studied example is the **vestibulo-ocular reflex** (VOR), which was a major focus of our discussions of sensorimotor integration (see chapter 12). Recall that the VOR prevents the image of the visual world on the retina from moving during passive or active movements of the head. To compensate for visual motion during head movements, the VOR moves the eyes within their sockets. The sensory information for the reflex derives from the motion sensors of the vestibular apparatus, in the semicircular canals of the inner ear. Within the brain, only a single relay interneuron (in the vestibular nuclei, just beneath the cerebellum) intervenes between the vestibular ganglion cells and the motor neurons of the eye muscles (Fig. 21.16).

One important consideration is that the VOR is an **open-loop reflex** (see chapter 12), operating without the benefit of immediate sensory feedback. Thus, the strength of synaptic interactions in the reflex circuit must be "calibrated" properly to ensure that the right amount of eye movement is produced (that is, the amount required to prevent image motion on the retina), given a particular velocity of head rotation. The performance of the VOR is constantly monitored, and the calibration of the reflex is updated appropriately to maintain a match between eye movement and head movement. In other words, the strength of synaptic connections in the VOR is based on experience and represents a form of learning. As we have seen, synaptic strength can be modified on either a short- or long-term basis by simple types of cellular learning mechanisms. In this section, we will examine the modifiability of the VOR from this perspective.

Figure 21.16
The basic circuit for the vestibulo-ocular reflex in the primate brain.



Learning in the VOR can be easily demonstrated. If an observer puts on a pair of eyeglasses that magnify the visual world, a mismatch suddenly arises between the eye movements produced by the VOR and the amount of movement required to keep the image in place on the retina. Without the magnifying eyeglasses, a rotation of the head to the right at 10°/s would produce movement of the image on the retina at 10°/s, if the eyes remain fixed in their sockets, staring straight ahead. Movement of the eyes to the left at 10°/s would exactly compensate for this head movement, keeping the image of the world at the same position on the retina. The VOR normally provides this service. When the observer puts on magnifying spectacles, however, the image projected onto the retina is larger than normal. As a result, rotation of the head at 10°/s produces movement of the image on the retina at *greater* than 10°/s. When the VOR produces its previously correct output of 10° of eye movement per second, the motion of the eyes will be insufficient to correct the slippage of the image on the retina, and the visual world will appear to move to the left as the head rotates to the right. With time, however, the output of the VOR increases until the image once again becomes stable on the retina as the head rotates. This change in the VOR is a form of learning.

We can conveniently express the relationship between the input (head rotation) and the output (eye rotation) of the VOR in terms of the gain of the reflex. The gain is simply the output velocity divided by the input velocity (both expressed in degrees per second). Under normal conditions, the correct gain would be 1.0, corresponding to equal head and eye rotation velocities. With magnifying eyeglasses, however, the required gain is greater than 1.0; with demagnifying glasses, the required gain is less than 1.0. As experience increases, the gain comes to closely match the required value when the magnification of the visual world is altered experimentally. This change of gain of the reflex is what we mean by VOR learning. In the absence of counterexperience, the modified gain of the VOR is retained indefinitely; thus, it represents a long-term change in synaptic processing.

The cerebellum in VOR learning

In chapter 11, we learned that the cerebellum is, in broad terms, involved in the modification of motor behavior based on sensory information about the outcome of the behavior. This function of the cerebellum is exemplified by the modification of the VOR to minimize image motion during head rotation. If the cerebellar cortex is removed surgically, the normal VOR is not affected very much (as expected from the circuit diagram shown in Figure 21.16). Without the cerebellum, however, VOR learning is abolished and the gain of the reflex cannot be modified based on experience.

It is not necessary to destroy the entire cerebellar cortex to prevent learning in the VOR. Like other parts of the brain, the cerebellum is regionally specialized for specific types of sensory and motor systems. The portion concerned with vestibular sensory information and eye movements is the **floccular complex** (which consists of the **flocculus**—a lobe at the most lateral part of the cerebellum on each side of the brain—and the **ventral paraflocculus**). Removal of the floccular complex is sufficient to abolish

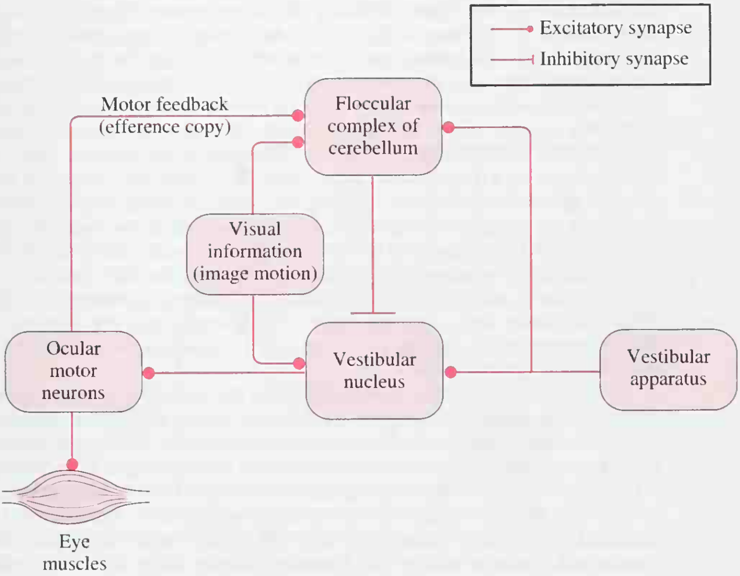
VOR plasticity. If the floccular complex is destroyed *after* the VOR has been modified, the modifications are mostly retained. If the normal optical conditions are restored (for example, magnifying eyeglasses are removed) after destruction of the floccular complex, the normal VOR cannot be restored. Thus, the cerebellum is required to *acquire* modifications of the VOR; once acquired, the altered VOR gain is *retained* at least in part by portions of the VOR circuitry outside the cerebellum.

Connections between the cerebellum and the VOR circuitry

Figure 21.17 summarizes the synaptic connections between the cerebellum and the VOR circuitry. The arrangement follows the general plan for cerebellar circuits presented in chapter 11: the sensory inputs project in parallel to the cerebellar cortex and to the deep cerebellar nuclei. In the case of the VOR, the floccular complex is the relevant part of the cerebellar cortex, and the vestibular nucleus is the relevant deep cerebellar nucleus. The output cells of

Figure 21.17

The floccular complex of the cerebellum influences synaptic transfer in the vestibular nucleus during the vestibulo-ocular reflex. The cerebellum receives excitatory inputs from the inputs that also excite the vestibular nucleus, including the vestibular sensory inputs and visual information about motion on the retina. Feedback from the motor output of the ocular motor neurons also reaches the cerebellum.



the cortex, the **Purkinje cells**, project back to the vestibular nucleus, where they make inhibitory synaptic connections.

The VOR utilizes two sources of sensory information: vestibular inputs give information about head rotation, and inputs derived from the visual system provide information about direction and velocity of image motion on the retina. The vestibular inputs inform the cerebellar cortex about head motion and supply the excitatory drive for the basic circuitry of the VOR (see Fig. 21.16). The visual inputs provide an error signal that indicates how successfully eye movements stabilize the image on the retina. A third input source for the cerebellum is a feedback signal from the motor neurons of the ocular muscles (see Fig. 21.17). This type of motor output signal, called **efference copy**, gives information about the output signal being sent to the eye muscles. The three signals to the cerebellum permit a comparison among head rotation velocity, image slippage on the retina, and strength of excitatory drive to the eye muscles.

Although the diagram of Figure 21.17 is specific for the VOR, the same general plan of signal connections is used for other sensory/motor combinations in other portions of the cerebellum. Consequently, the calculation of a correction signal, like that thought to be carried out for the VOR, may be carried out in other parts of the cerebellum for different motor systems.

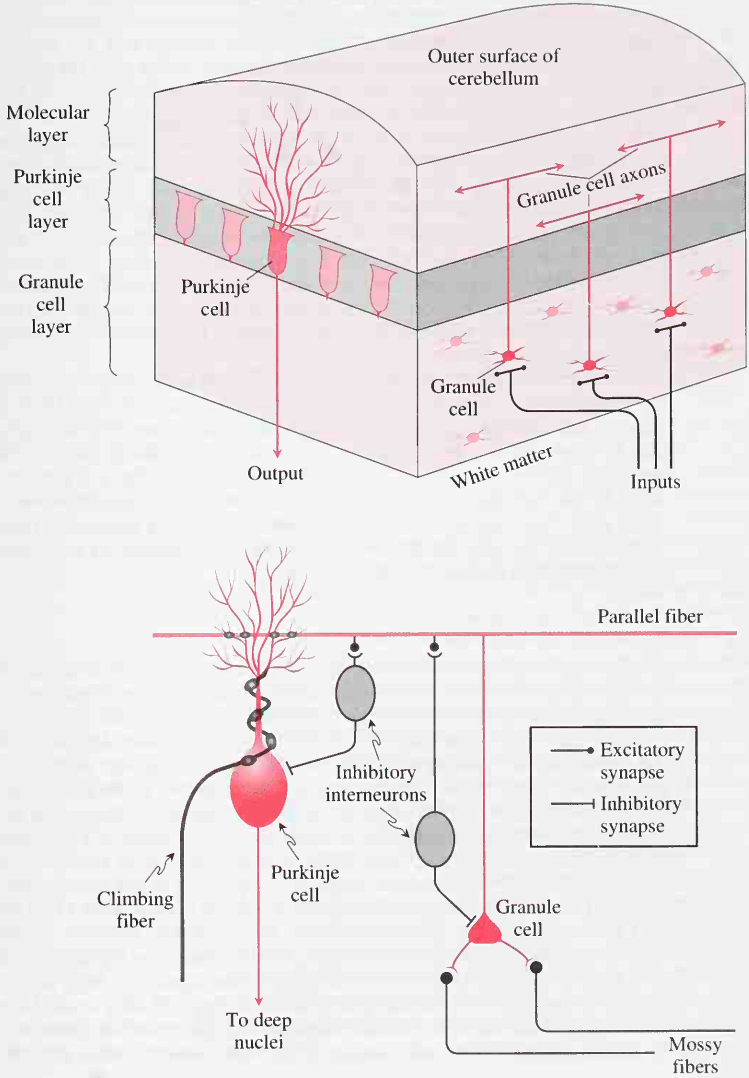
Synaptic circuitry within the cerebellar cortex

The pattern of synaptic connections among the neurons of the floccular complex (Fig. 21.18) is also found throughout the cerebellar cortex. Incoming axons are of two types, **climbing fibers** and **mossy fibers**, which are distinguished on the basis of their distinctive synaptic connections. Climbing fibers synapse exclusively on Purkinje cells, which are the large neurons whose axons represent the sole output from the cerebellum. Mossy fibers make contact with **granule cells**, which are smaller interneurons whose cell bodies are located deeper in the cerebellum than the Purkinje cells. Both types of fibers make excitatory synapses onto their target neurons. Granule cells give rise to a single axon, which extends toward the surface of the cerebellum and then bifurcates, sending out branches, called **parallel fibers**, parallel to the surface for long distances. The dendrites of the Purkinje cells extend toward the surface into the space where the parallel fibers ramify. As the parallel fibers intersect the dendrites of Purkinje cells, they form excitatory synapses. In addition to these excitatory interactions, inhibitory connections are made onto Purkinje cells and granule cells by inhibitory interneurons (stellate, basket, and Golgi cells), which receive excitatory inputs from the parallel fibers.

In the floccular complex, mossy fibers carry the vestibular sensory inputs, while the visual information arrives via both mossy fibers and climbing fibers. The efference-copy feedback from the oculomotor output is transmitted via mossy fibers. It is not clear whether the different types of incoming information on mossy fibers are segregated to different sets of granule cells.

It is also not known how the synaptic interconnections summarized in Figure 21.18 compare vestibular, visual, and motor inputs to generate an error signal. Purkinje cells of the floccular complex show little change in

Figure 21.18
Synaptic interactions in the cerebellum.



action potential activity during the VOR under normal conditions, when the gain of the reflex is at its normal value of 1.0. Although ongoing activity of the Purkinje cells provides a tonic level of inhibitory input to the neurons of the vestibular nucleus, the firing rate of the Purkinje cells neither increases nor decreases during the VOR. Thus, the inhibitory input from Purkinje cells to the vestibular relay neurons of the vestibular nucleus does not change under normal conditions during the reflex. However, when the VOR gain is lower than normal as a result of training (that is, gain less than 1.0), the floccular Purkinje cells increase their rate of firing during the VOR. This increases inhibition of the neurons in the vestibular nucleus during the reflex, diminishing the excitatory drive provided to the oculomotor neurons. Conversely, the firing rate of the Purkinje cells decreases during the VOR when the gain is higher than normal (that is, gain greater than 1.0). This decreased activity of Purkinje cells reduces inhibition of the vestibular nucleus neurons during the VOR and causes greater excitatory drive to be transmitted to the oculomotor neurons. The changes in the inhibitory action of the Purkinje cells under conditions of modified gain thus contribute to the changes in excitation from the vestibular nucleus to the oculomotor neurons during the modified reflex.

Although the inhibition-related changes from the Purkinje cells may contribute to the acquisition of the modified reflex during learning, the fact remains that learned changes in VOR gain persist when the floccular complex is destroyed and the inhibitory input from the Purkinje cells to the vestibular nucleus is removed. Thus, changes in the inhibitory input provided by the Purkinje cells cannot account for retention of modification in reflex gain. This suggests that changes in synaptic efficacy within the basic VOR circuitry (see Fig. 21.16) are at least partly responsible for long-term storage of learned changes in reflex strength.

Long-term depression in Purkinje cells

The long-term changes in synaptic strength in the VOR are reminiscent of LTP and LTD, which were discussed earlier in this chapter. Considerable attention has been directed toward understanding LTD in the excitatory synapses made onto cerebellar Purkinje cells by parallel fibers. Activation of the climbing-fiber input to a Purkinje cell produces a long-term decrease in the synaptic effect of parallel-fiber inputs that are active at the same time. Thus, concurrent activation of climbing fibers produces an associative depression of parallel-fiber synapses. A single action potential in a climbing fiber produces a large e.p.s.p. and an increase in intracellular calcium in a Purkinje cell; these modifications trigger the depression of the coactive parallel-fiber synapses in a manner thought to be similar to associative LTP. This LTD mechanism might potentially allow an interaction between signals derived from motion of the visual image (climbing fibers) and signals derived from vestibular inputs (a portion of the parallel-fiber inputs). In turn, altered activity of Purkinje cells during modification of the VOR may result from these synaptic interactions. Because destruction of the cerebellar cortex fails to abolish previously learned changes in the VOR, however, other synaptic sites outside the cerebellum must be involved in the storage of the learned changes.

Examination of the diagram in Figure 21.17 suggests that the vestibular nucleus might be another site at which all relevant sensory and motor information is represented. LTP and LTD of synaptic responses in neurons of the vestibular nucleus could produce the changes in synaptic strength required to alter the overall gain of the reflex. The cerebellar output to the vestibular nucleus might then be necessary in some way to set up the long-term changes in synaptic efficacy within the vestibular nucleus. At present, no evidence is available on the plasticity of the synaptic connections in the vestibular nucleus. Because the sites of long-term alteration in synaptic strength within the VOR circuitry are not yet established, it remains impossible to identify the cellular and molecular mechanisms that give rise to and sustain the modifications of the VOR. Although the VOR is one of the simplest reflex circuits in the primate central nervous system, the state of knowledge of mechanisms of plasticity is primitive compared with reflex plasticity in *Aplysia,* for example. It should be interesting to monitor future progress in understanding the molecular changes underlying synaptic plasticity in simple systems such as *Aplysia*, in mammalian models such as the hippocampus, and in primate reflexes like the VOR.

SUMMARY

Synaptic connections among neurons change in strength over time, giving rise to both short-term and long-term changes in the behavior of the organism. This is true for both complex neural circuits and simple reflexes.

Activity-dependent changes in synaptic effectiveness within a single synaptic terminal are the simplest type of synaptic plasticity. An action potential in a presynaptic terminal leaves an aftereffect that alters the amount of neurotransmitter released by subsequent action potentials. This aftereffect can either enhance or depress the subsequent release of neurotransmitter. Short-term enhancement mechanisms include the following processes: facilitation, which is triggered by a small number of presynaptic action potentials and lasts for a few hundred milliseconds; augmentation, which lasts for several seconds and is triggered after action potentials are fired at a high rate for a few seconds; and potentiation, which is triggered by still-longer periods of high-frequency firing and lasts for minutes. Short-term enhancement is triggered by a buildup of calcium ions inside the presynaptic terminal during bursts of action potentials. Short-term depression of neurotransmitter release can also occur after a burst of presynaptic action potentials. Multiple mechanisms of depression have been identified, including calcium-dependent inactivation or activation of ion channels, depletion of releasable synaptic vesicles, and activation of autoreceptors on the synaptic terminal by neurotransmitter released from the same terminal.

Long-term changes in synaptic strength last for days or weeks, rather than minutes. Long-term potentiation (LTP) has been studied extensively in the hippocampus, a brain region suspected to be involved in the formation of memories. LTP occurs when a synaptic input is activated at the same time as the postsynaptic cell is depolarized, which normally occurs only during a period of strong synaptic activation. Thus, LTP requires the *association* between the activation of an input and the postsynaptic state of the receiving neuron. The potentiated synaptic input then produces a larger-than-normal excitatory postsynaptic potential, an effect that lingers for days or weeks. LTP is thought to be triggered by the influx of calcium ions through postsynaptic glutamate receptors, called NMDA receptors, that require both glutamate and postsynaptic depolarization to open. The increase in postsynaptic calcium triggers cellular messengers that enhance future transmission via both presynaptic and postsynaptic changes. These changes remain localized to the activated synapse. Some synapses in the central nervous system also show long-term depression (LTD), but the conditions for initiating LTD are less clearly established.

Cellular mechanisms of learning in simple reflexes have been studied extensively using withdrawal reflexes in a marine mollusc, *Aplysia californica*. Habituation of a reflex refers to the progressive decline in vigor of the reflexive response with repeated presentations of the eliciting stimulus. In the withdrawal reflex, habituation results from synaptic depression in the excitatory synapses in the reflex circuit. Sensitization is the enhancement of a reflex following contact with a noxious stimulus. Sensitization of the withdrawal reflex in *Aplysia* occurs when facilitatory interneurons are stimulated by the noxious stimulus. These neurons release the neurotransmitter serotonin, which acts via G-protein–coupled receptors to increase the concentration of the second messenger, cyclic AMP, inside the excitatory synaptic terminals of the withdrawal-reflex circuit. The cAMP induces phosphorylation of potassium channels, which then become inactivated. Presynaptic action potentials then have a longer duration, causing greater calcium influx during an action potential and greater neurotransmitter release at the excitatory synapses that elicit the withdrawal response.

Reflexive learning is also observed in the primate central nervous system. For example, learning occurs in the vestibulo-ocular reflex (VOR), which moves the eyes in such a way as to keep the visual image stable on the retina when the head rotates. The strength of the motor output to the eye muscles is adjusted based on experience, if the output does not maintain a stabilized retinal image. This reflex learning reflects changes in the strength of synaptic connections in the reflex circuit. The cerebellum is required for learning in the VOR.

Appendix A: Derivation of the Nernst Equation

The Nernst equation is used extensively in the discussion of resting membrane potential and action potentials in this book. The derivation presented here is necessarily mathematical and requires some knowledge of differential and integral calculus to understand thoroughly. However, I have tried to explain the meaning of each step in words; this approach is intended to allow those without the necessary background to follow the logic qualitatively.

This derivation of the Nernst equation uses equations for the movement of ions down concentration and electrical gradients to arrive at a quantitative description of the equilibrium condition. The starting point is the realization that at equilibrium there will be no net movement of the ion across the membrane. That is, in the presence of both concentrational and electrical gradients, the rate of movement of the ion down the concentration gradient is equal and opposite to the rate of movement of the ion down the electrical gradient. For a charged substance (an ion), movement across the membrane constitutes a transmembrane electrical current, I. Thus, at equilibrium

$$I_C = -I_E \tag{A.1}$$

or

$$I_C + I_E = 0 \tag{A.2}$$

where I_C and I_E are the currents due to the concentrational and electrical gradients, respectively.

CONCENTRATIONAL FLUX

Consider first the current due to the concentration gradient, which will be given by

$$I_C = A\Phi_C ZF \tag{A.3}$$

In words, Equation (A.3) states that the current through the membrane of area A will be equal to the flux, Φ_C, of the ion down the concentration gradient (number of ions per second per unit area of membrane) multiplied by Z (the valence of the ion) and F (Faraday's constant; 96,500 coulombs per mole of univalent ion). The factor ZF translates the flux of ions into flux of charge and hence into an electrical current. The flux Φ_C for a given ion (call the ion Y, for example) will depend on the concentration gradient of Y across the membrane (that is, $[Y]_{in} - [Y]_{out}$) and on the membrane permeability to Y, p_Y. Quantitatively, this relation is given by

$$\Phi_C = p_Y([Y]_{in} - [Y]_{out}) \tag{A.4}$$

Note that p_Y has units of velocity (cm/s), so Φ_C has units of molecules/s/cm^2 (remember that [Y] has units of molecules/cm^3). The permeability coefficient, p_Y, is in turn given by

$$p_Y = D_Y/a \tag{A.5}$$

where D_Y is the diffusion constant for Y within the membrane and a is the thickness of the membrane. D_Y can be expanded to yield

$$D_Y = uRT \tag{A.6}$$

where u is the mobility of the ion within the membrane and RT (the gas constant times the absolute temperature) is the thermal energy available to drive ion movement. Substituting Equation (A.6) in (A.5) and the result in Equation (A.4) yields

$$\Phi_C a = uRT([Y]_{in} - [Y]_{out}) \tag{A.7}$$

Equation (A.7) gives us the flux through a membrane of thickness a, but we would like a more general expression that gives us the flux through any arbitrary plane in the presence of a concentration gradient. To arrive at this expression, consider the situation diagrammed in Figure A.1, which shows a segment of membrane separating two compartments. The dimension perpendicular to the membrane is called x, and the membrane extends from 0 to a (thickness = a). In this situation, Equation (A.7) can be expressed in the form of an integral equation:

$$\Phi_C\left(\int_0^a dx\right) = uRT\left(\int_0^a dC\right) \tag{A.8}$$

Here, C stands for the concentration of the ion; therefore, in reference to Figure A.1, C_a is $[Y]_{in}$ and C_0 is $[Y]_{out}$. Differentiating both sides of Equation (A.8) yields

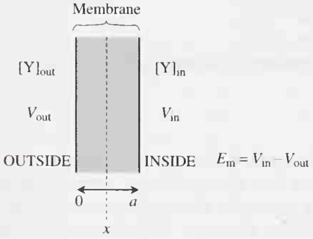
$$\Phi_C\, dx = uRT\, dC \tag{A.9}$$

which can be arranged to give the more general form of Equation (A.7) that we desire:

$$\Phi_C = uRT\left(\frac{dC}{dx}\right) \tag{A.10}$$

Equation (A.10) can be substituted into Equation (A.3) to give the ionic current due to the concentration gradient.

Figure A.1
Segment of membrane separating two compartments.



CURRENT DUE TO ELECTRICAL GRADIENT

Return now to the current driven by the electrical gradient, which can be expressed

$$I_E = A\Phi_E ZF \tag{A.11}$$

The flux, Φ_E, of a charged particle through a plane at position x in the presence of a voltage gradient dV/dx will be

$$\Phi_E = uZFC\left(\frac{dV}{dx}\right) \tag{A.12}$$

Again, u is the mobility of the ion, and C is the concentration of the ion at position x. The factor ZFC is then the concentration of charge at the location of the plane; this factor is necessary because the voltage gradient dV/dx acts on charge and ZFC gives the "concentration" of charge at position $= x$. Equation (A.12) is analogous to Equation (A.10), except that the voltage gradient rather than the concentration gradient is of interest.

TOTAL CURRENT AT EQUILIBRIUM

Equations (A.12), (A.11), (A.10), and (A.3) can be combined into the form of Equation (A.2) to give

$$uAZF\left(RT\frac{dC}{dx} + ZFC\frac{dV}{dx}\right) = 0 \tag{A.13}$$

This expression requires that

$$RT\left(\frac{dC}{dx}\right) = -ZFC\left(\frac{dV}{dx}\right) \tag{A.14}$$

Equation (A.14) can be rearranged to give a differential equation that can be solved for the equilibrium voltage gradient:

$$\left(-\frac{RT}{ZF}\right)\left(\frac{dC}{C}\right) = dV \tag{A.15}$$

This equation can be solved for V by integrating across the membrane. Using the nomenclature of Figure A.1, the integrals are

$$-\frac{RT}{ZF}\int_{[\mathrm{Y}]_{\mathrm{out}}}^{[\mathrm{Y}]_{\mathrm{in}}} \frac{dC}{C} = \int_{\mathrm{V}_{\mathrm{out}}}^{\mathrm{V}_{\mathrm{in}}} dV \tag{A.16}$$

The solution to these definite integrals is

$$-\frac{RT}{ZF}(\ln[\mathrm{Y}]_{\mathrm{in}} - \ln[\mathrm{Y}]_{\mathrm{out}}) = V_{\mathrm{in}} - V_{\mathrm{out}} \tag{A.17}$$

or

$$\frac{RT}{ZF}\ln\left(\frac{[\mathrm{Y}]_{\mathrm{out}}}{[\mathrm{Y}]_{\mathrm{in}}}\right)=V_{\mathrm{in}}-V_{\mathrm{out}}=E_{\mathrm{M}} \tag{A.18}$$

Equation (A.18) is the Nernst equation.

Appendix B: Derivation of the Goldman Equation

The Goldman equation, or constant-field equation, is important for understanding the factors that govern the steady-state membrane potential. As discussed in chapter 4, the Goldman equation describes the nonequilibrium membrane potential reached when two or more ions with unequal equilibrium potentials are free to move across the membrane. The basic strategy in this derivation is to use the flux equations derived in Appendix A to solve separately for the ionic current carried by each permeant ion and then to set the sum of all ionic currents equal to zero. The derivation is somewhat more complex than that of the Nernst equation in Appendix A, and it requires some knowledge of differential and integral calculus to follow in detail. Nevertheless, it should be possible for those without the necessary mathematics to follow the logic of the steps and thus to gain some insight into the physical mechanisms described by the equation.

When several ions are moving across the membrane simultaneously, a steady value of membrane potential will be reached when the sum of the ionic currents carried by the individual ions is zero; that is, for permeant ions A, B, and C

$$I_A + I_B + I_C = 0 \tag{B.1}$$

The first step in arriving at a value of membrane potential that satisfies this condition is to solve for the net ionic flux, Φ, for each ion separately. The total flux for a particular ion will be the sum of the flux due to the concentration gradient and the flux due to the electrical gradient:

$$\Phi_T = \Phi_C + \Phi_V \tag{B.2}$$

The expressions for Φ_C and Φ_V are given by Equations (A.10) and (A.12) in Appendix A. Thus, Equation (B.2) becomes

$$\Phi_T = uRT(dC/dx) + uZFC(dV/dx) \tag{B.3}$$

If it is assumed that the electric field across the membrane is constant (this is the constant-field assumption from which the equation draws its alternative name) and that the thickness of the membrane is *a*, then

$$dV/dx = V/a \tag{B.4}$$

In that case, Equation (B.3) can be written

$$\frac{\Phi_{\mathrm{T}}}{uRT} = \frac{dC}{dx} + \frac{ZFV}{RTa}C \tag{B.5}$$

This expression is a differential equation of the form

$$Q = \frac{dC}{dx} + P(x)C$$

which has a solution

$$C\exp\left(\int P(x)dx\right) = \int Q\exp\left(\int P(x)dx\right)dx + \text{constant} \tag{B.6}$$

In this instance, $Q = \Phi_{\mathrm{T}}/(uRT)$ and $P(x) = (ZFV)/(RTa)$. Making these substitutions and integrating Equation (B.6) across the membrane of thickness a (that is, from 0 to a) gives

$$C\exp\left(\frac{ZFV}{RTa}\right)\Bigg|_0^a = \frac{\Phi_{\mathrm{T}}}{uRT}\int_0^a \exp\left(\frac{ZFVx}{RTa}\right)dx \tag{B.7}$$

This expression becomes

$$C_a\exp\left(\frac{ZFV}{RT}\right) - C_0 = \frac{\Phi_{\mathrm{T}}}{uRT}\left[\exp\left(\frac{ZFVx}{RTa}\right)\Big/\left(\frac{ZFV}{RTa}\right)\right]\Bigg|_0^a$$

or

$$C_a\exp\left(\frac{ZFV}{RT}\right) - C_0 = \frac{\Phi_{\mathrm{T}}}{uRT}\frac{RTa}{ZFV}\left[\exp\left(\frac{ZFVa}{RTa}\right) - \exp\left(\frac{ZFV\cdot 0}{RTa}\right)\right]$$

Rearranging and combining terms yields

$$C_a\exp\left(\frac{ZFV}{RT}\right) - C_0 = \frac{\Phi_{\mathrm{T}}a}{uZFV}\left[\exp\left(\frac{ZFV}{RT}\right) - 1\right]$$

This expression can be solved for Φ_{T} to yield

$$\Phi_{\mathrm{T}} = \frac{uZFV}{a}\left[\frac{C_a\exp(ZFV/RT) - C_0}{\exp(ZFV/RT) - 1}\right] \tag{B.8}$$

Now, C_a and C_0 are the concentrations of the ion just within the membrane. These concentrations are related to the concentrations in the fluids inside and outside the cell by $C_a = \beta C_{\mathrm{in}}$ and $C_0 = \beta C_{\mathrm{out}}$, where β is the oil–water partition coefficient for the ion in question. Substituting these parameters in Equation (B.8) gives

$$\Phi_{\mathrm{T}} = \frac{\beta uZFV}{a}\left[\frac{C_{\mathrm{in}}\exp(ZFV/RT) - C_{\mathrm{out}}}{\exp(ZFV/RT) - 1}\right] \tag{B.9}$$

The permeability constant, p_i, for a particular ion is given by $p_i = \beta uRT/a$, or $p_i/RT = \beta u/a$. Making this substitution in Equation (B.9) gives

$$\Phi_T = \frac{p_i ZFV}{RT}\left[\frac{C_{in}\exp(ZFV/RT) - C_{out}}{\exp(ZFV/RT) - 1}\right] \tag{B.10}$$

The flux, Φ_T, for an ion can be converted to a flow of electrical current, as required in Equation (B.1), by multiplying by ZF (the number of coulombs per mole of ion); therefore

$$I = \frac{p_i Z^2F^2V}{RT}\left[\frac{C_{in}\exp(ZFV/RT) - C_{out}}{\exp(ZFV/RT) - 1}\right] \tag{B.11}$$

This expression is needed for each ion in Equation (B.1). For instance, if the three permeant ions are Na, K, and Cl with permeabilities p_{Na}, p_K, and p_{Cl}, then Equation (B.1) becomes (keeping in mind that the valence of chloride is -1)

$$\frac{F^2V}{RT}\left[\frac{p_K([\mathrm{K}]_{in}e^{FV/RT} - [\mathrm{K}]_{out}) + p_{Na}([\mathrm{Na}]_{in}e^{FV/RT} - [\mathrm{Na}]_{out})}{\exp(FV/RT) - 1} + \frac{p_{Cl}([\mathrm{Cl}]_{in}e^{-FV/RT} - [\mathrm{Cl}]_{out})}{\exp(-FV/RT) - 1}\right] = 0$$

Multiplying through by $-\exp(FV/RT)/-\exp(FV/RT)$ and rearranging yields

$$\frac{F^2V}{RT(\exp(FV/RT) - 1}[(p_K[\mathrm{K}]_{in} + p_{Na}[\mathrm{Na}]_{in} + p_{Cl}[\mathrm{Cl}]_{out})e^{FV/RT} - (p_K[\mathrm{K}]_{out} + p_{Na}[\mathrm{Na}]_{out} + p_{Cl}[\mathrm{Cl}]_{in})] = 0$$

This expression requires that

$$(p_K[\mathrm{K}]_{in} + p_{Na}[\mathrm{Na}]_{in} + p_{Cl}[\mathrm{Cl}]_{out})e^{FV/RT} - (p_K[\mathrm{K}]_{out} + p_{Na}[\mathrm{Na}]_{out} + p_{Cl}[\mathrm{Cl}]_{in}) = 0$$

or

$$e^{FV/RT} = \frac{(p_K[\mathrm{K}]_{out} + p_{Na}[\mathrm{Na}]_{out} + p_{Cl}[\mathrm{Cl}]_{in})}{(p_K[\mathrm{K}]_{in} + p_{Na}[\mathrm{Na}]_{in} + p_{Cl}[\mathrm{Cl}]_{out})}$$

Taking the natural logarithm of both sides and solving for V yields the usual form of the Goldman equation

$$V = \frac{RT}{F}\ln\left(\frac{p_K[\mathrm{K}]_{out} + p_{Na}[\mathrm{Na}]_{out} + p_{Cl}[\mathrm{Cl}]_{in}}{p_K[\mathrm{K}]_{in} + p_{Na}[\mathrm{Na}]_{in} + p_{Cl}[\mathrm{Cl}]_{out}}\right)$$

Suggested Readings

In a rapidly developing field like neurobiology, students should be prepared to do some spadework to update themselves on recent advances. I will start by suggesting some particular journals and review series that typically include articles on the topics covered in this book. In addition, topical searches of the catalogs of your local library (and on-line library catalogs) can turn up recent specialty volumes, which are often based on international conferences and symposia.

Annual Reviews, Inc. publishes yearly volumes in several scientific disciplines. Articles relevant to this book are commonly found in *Annual Review of Neuroscience, Annual Review of Physiology, Annual Review of Biophysics and Biomolecular Structure, Annual Review of Biochemistry,* and *Annual Review of Cell Biology.*

Current Opinion in Neurobiology publishes monthly issues, each organized around a particular theme. Articles are brief and emphasize recent findings.

Physiological Reviews is a periodical published by the American Physiological Society. Articles are usually long and comprehensive reviews of a special topic, and issues frequently include coverage of cellular and molecular neurobiology.

Scientific American publishes well-illustrated reviews written primarily for a general readership. These articles often provide a good starting point for further reading.

Trends in Neurosciences presents brief, up-to-date reviews on very specific topics. These articles are usually good starting points for more in-depth reading. Other "Trends in . . ." series (*Trends in Biochemical Sciences, Trends in Cell Biology,* and *Trends in Pharmacological Sciences*) sometimes include articles of interest to neurobiologists.

Rating system

(*): Introductory level; for a general, nonscientist audience or beginning students.

(**): Intermediate level; a general review for nonspecialists or second-level students.

(***): Advanced level; for advanced students wishing greater detail.

(****): Original research articles; usually intended for specialists working in the field.

Chapter 1: An Overview of Neurobiology

Hall JW, ed. An introduction to molecular neurobiology. Sunderland, MA: Sinauer, 1992. (**)

Hille B. Ionic channels of excitable membranes, 2nd ed. Sunderland, MA: Sinauer, 1992. (***)

Kandel ER, Schwartz JH, Jessell TM, eds. Principles of neural science. New York: Elsevier, 1991. (***)

Katz B. Nerve, muscle and synapse. New York: McGraw-Hill, 1966. (**)

Levitan IB, Kaczmarek LK. The neuron, cell and molecular biology. New York: Oxford University Press, 1991. (**)

Matthews GG. Cellular physiology of nerve and muscle. 3rd ed. Cambridge, MA: Blackwell Scientific Publications, 1998. (*)

Chapter 2: Organization of Nervous Systems

Anderson PAV. Ionic currents of the Scyphozoa. In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989:267–280. (****)

Arbas EA, Meinertzhagen IA, Shaw SR. Evolution in nervous systems. Ann Rev Neuroscience 1991;14:9–38. (***)

Carr WES. Chemical signaling in lower organisms: a prelude to the evolution of chemical communication in the nervous system. In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989:81–94. (****)

Cowan WM. The development of the brain. Scientific American 1979;241/3:112–133. (*)

Guthrie S. The status of the neural segment. Trends Neurosciences, 1995;18:74–79. (**)

Hennessey TM. Ion currents of *Paramecium:* effects of mutations and drugs. In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989:215–235. (****)

Kimmel CB. Patterning the brain of the zebrafish embryo. Ann Rev Neuroscience 1993;16:707–732. (***)

Krubitzer L. The organization of neocortex in mammals—are species differences really so different. Trends Neuroscience 1995;18:408–417. (**)

Kung C. Ion channels of unicellular microbes. In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989;203–214. (****)

Martin JH. Neuroanatomy: text and atlas. New York: Elsevier, 1989. (***)

Meech RW. The electrophysiology of swimming in the jellyfish *Aglantha digitale.* In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989:281–298. (****)

Nauta WJH, Feirtag M. Fundamental neuroanatomy. New York: Freeman, 1986. (**)

Purves D, Lichtman JW. Principles of neural development. Sunderland, MA: Sinauer, 1985. (**)

Rakic P. A small step for the cell, a giant leap for mankind—a hypothesis of neocortical expansion during evolution. Trends Neuroscience 1995; 18:383–388. (**)

Spencer AN. Chemical and electrical synaptic transmission in the Cnidaria. In: Anderson PAV, ed. Evolution of the first nervous systems. New York: Plenum Press, 1989:33–53. (****)

Chapter 3: Osmotic Balance and the Maintenance of Cell Volume

Bretscher MS. The molecules of the cell membrane. Scientific American 1985;253:4, 100–108. (*)

Burton RF. The composition of animal cells: solutes contributing to osmotic pressure and charge balance. Comp Biochem Physiol [B] 1983;76:663–671. (****)

Fettiplace R, Haydon DA. Water permeability of lipid membranes. Physiol Rev 1980;60:510–550. (****)

Gilles R. Mechanisms of osmoregulation: maintenance of cell volume. New York: Wiley, 1979. (***)

Kwon HM, Handler JS. Cell volume regulated transporters of compatible osmolytes. Curr Opinion Cell Biol 1995;7:465–471. (**)

MacKnight AD. Principles of cell volume regulation. Renal Physiol Biochem 1988;11:114–141. (****)

MacKnight ADC, Leaf A. Regulation of cell volume. Physiol Rev 1977;57:510–573. (***)

Orgel LE. The origin of life on the earth. Scientific American 1994;271:76–83. (*)

Potts WT. Osmotic and ionic regulation. Ann Rev Physiol 1968;30:73–104. (***)

Singer SJ. The molecular organization of membranes. Ann Rev Biochem 1974;43:805–833. (***)

Verkman AS. Water channels in cell membranes. Ann Rev Physiol 1992;54:97–108. (***)

Chapter 4: Origin of Electrical Membrane Potential

Fambrough DM, Lemas MV, Hamrick M, Emerick M, Renaud KJ, Inman EM, Hwang B, Takeyasu K. Analysis of subunit assembly of the Na-K-ATPase. Am J Physiol 1994;266:C579–C589. (****)

Glynn IM. How does the sodium pump pump? Soc General Physiol Series 1988;43:1–17. (***)

Hille B. Ionic channels of excitable membranes, 2nd ed. Sunderland, MA: Sinauer, 1992. (***)

Hodgkin AL, Horowicz P. The influence of potassium and chloride ions on the membrane potential of single muscle fibers. J Physiol 1959;148:127–160. (****)

Hodgkin AL, Katz B. The effect of sodium ions on the electrical activity of the giant axon of the squid. J Physiol 1949;108:37–77. (****)

Hodgkin AL, Keynes RD. Active transport of cations in giant axons from *Sepia* and *Loligo*. J Physiol 1955;128:28–60. (****)

Kaplan JH. Ion movements through the sodium pump. Ann Rev Physiol 1985;47:535–544. (***)

Katz B. Nerve, muscle, and synapse. New York: McGraw-Hill, 1966. (**)

Levitt DG. The mechanism of the sodium pump. Biochimica et Biophysica Acta 1980;604:321–345. (****)

Neher E, Sakmann B, eds. Single channel recording, 2nd ed. New York: Plenum, 1995. (***)

Sather WA, Yang J, Tsien RW. Structural basis of ion channel permeation and selectivity. Curr Opinion Neurobiol 1994;4:313–323. (**)

Thomas RC. Electrogenic sodium pump in nerve and muscle cells. Physiol Rev 1972;52:563–594. (***)

Wallick ET, Lane LK, Schwartz A. Biochemical mechanism of the sodium pump. Ann Rev Physiol 1979;41:397–411. (***)

Chapter 5: Generation of Nerve Action Potential

Armstrong CM. Voltage-dependent ion channels and their gating. Physiol Rev 1992;72:S5–S13. (***)

Bezanilla F, Stefani E. Voltage-dependent gating of ionic channels. Ann Rev Biophysics Biomolec Struc 1994;23:819–846. (****)

Catterall WA. Cellular and molecular biology of voltage-gated sodium channels. Physiol Rev 1992;72:S15–S48. (***)

Catterall WA. Structure and function of voltage-gated ion channels. Ann Rev Biochem 1995;64:493–531. (***)

Hille B. Ionic channels of excitable membranes, 2nd ed. Sunderland, MA: Sinauer, 1992. (***)

Kallen RG, Cohen SA, Barchi RL. Structure, function, and expression of voltage-dependent sodium channels. Molec Neurobiol 1993;7:383–428. (****)

Neher E, Sakmann B. The patch clamp technique. Scientific American 1992;266:3, 28–35. (*)

Pallotta BS, Wagoner PK. Voltage-dependent potassium channels since Hodgkin and Huxley. Physiol Rev 1992;72:S49–S67. (***)

Tasaki I. Conduction of impulses in the myelinated nerve fiber. Cold Spring Harbor Symposia on Quantitative Biology 1952;XVII:37–41. (****)

Waxman SG, Ritchie JM. Molecular dissection of the myelinated axon. Ann Neurol 1993;33:121–136. (****)

Chapter 6: The Action Potential: Voltage-Clamp Experiments

Hille B. Ionic channels of excitable membranes, 2nd ed. Sunderland, MA: Sinauer, 1992. (***)

Hodgkin AL, Huxley AF. Currents carried by sodium and potassium ions through the membrane of the giant axon of *Loligo*. J Physiol 1952; 116:449–472. (****)

Hodgkin AL, Huxley AF. The components of membrane conductance in the giant axon of *Loligo*. J Physiol 1952;116:473–496. (****)

Hodgkin AL, Huxley AF. The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. J Physiol 1952;116:497–506. (****)

Hodgkin AL, Huxley AF. Quantitative description of membrane current: its application to conduction and excitation in nerve. J Physiol 1952; 117:500–544. (****)

Hodgkin AL, Huxley AF. Movement of sodium and potassium ions during nervous activity. Cold Spring Harbor Symposia on Quantitative Biology 1952;XVII:43–52. (***)

Chapter 7: Synaptic Transmission at the Neuromuscular Junction

Augustine GJ, Charlton MP, Smith SJ. Calcium action in synaptic transmitter release. Ann Rev Neuroscience 1987;10:633–693. (***)

Augustine GJ, Burns ME, DeBello WM, Pettit DL, Schweizer FE. Exocytosis—proteins and perturbations. Ann Rev Pharmacol Toxicol 1996;36:659–701. (***)

Bennett MK, Scheller RH. A molecular description of synaptic vesicle membrane trafficking. Ann Rev Biochem 1994;63:63–100. (***)

Bertolino M, Llinas RR. The central role of voltage-activated and receptor-activated calcium channels in neuronal cells. Ann Rev Pharmacol Toxicol 1992;32:399–421. (***)

Calakos N, Scheller RH. Synaptic vesicle biogenesis, docking, and fusion—a molecular description. Physiol Rev 1996;76:1–29. (***)

Del Castillo J, Katz B. Quantal components of the end-plate potential. J Physiol 1954;124:560–573. (****)

Dunlap K, Luebke JI, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. Trends Neurosciences 1995;18:89–98. (**)

Fatt P, Katz B. Spontaneous subthreshold activity at motor nerve endings. J Physiol 1952;117:109–128. (****)

Heuser JE. Review of electron microscopic evidence favoring vesicle exocytosis as the structural basis for quantal release during synaptic transmission. Quart J Experimental Physiol 1989;74:1051–1069. (***)

Heuser JE, Reese TS. Structural changes after transmitter release at the frog neuromuscular junction. J Cell Biol 1981;88:564–580. (****)

Jahn R, Sudhof TC. Synaptic vesicles and exocytosis. Ann Rev Neuroscience 1994;17:219–246. (**)

Katz B. Quantal mechanism of neural transmitter release. Science 1971; 173:123–126. (**)

Katz B, Miledi R. The timing of calcium action during neuromuscular transmission. J Physiol 1967;189:535–544. (****)

Matthews G. Neurotransmitter release. Ann Rev Neuroscience 1996;19:219–233. (***)

Nicholls DG. Proteins, transmitters and synapses. Oxford: Blackwell Scientific Publications, 1994. (**)

Tsien RW, Lipscombe D, Madison D, Bley K, Fox A. Reflections on Ca^{2+}-channel diversity, 1988–1994. Trends Neurosciences 1995;18:52–54. (**)

Van der Kloot W, Molgo J. Quantal acetylcholine release at the vertebrate neuromuscular junction. Physiol Rev 1994;74:899–991. (***)

Chapter 8: Synaptic Transmission in the Central Nervous System

Brown DA. G-proteins and potassium currents in neurons. Ann Rev Physiol 1990;52:215–242. (***)

Catterall WA. Molecular properties of a superfamily of plasma-membrane cation channels. Curr Opinion Cell Biol 1994;6:607–615. (**)

Clapham DE. Direct G protein activation of ion channels? Ann Rev Neuroscience 1994;17:441–464. (***)

Coombs JS, Eccles JC, Fatt P. Excitatory synaptic action in motoneurones. J Physiol 1955;130:374–395. (****)

Dunlap K, Luebke JI, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. Trends Neurosciences 1995;18:89–98. (**)

Gilman AG. G proteins: transducers of receptor-generated signals. Ann Rev Biochem 1987;56:615–649. (**)

Hamm HE, Gilchrist A. Heterotrimeric G proteins. Curr Opinion Cell Biol 1996;8:189–196. (**)

Kennedy MB. The biochemistry of synaptic regulation in the central nervous system. Ann Rev Biochem 1994;63:571–600. (***)

Levitan IB. Modulation of ion channels by protein phosphorylation and dephosphorylation. Ann Rev Physiol 1994;56:193–212. (***)

Linder ME, Gilman AG. G proteins. Scientific American 1992;267:1, 56–61. (*)

MacDonald RL, Olsen RW. $GABA_A$ receptor channels. Ann Rev Neuroscience 1994;17:569–602. (***)

Matthews G, Wickelgren WO. Glycine, GABA and synaptic inhibition of reticulospinal neurones of lamprey. J Physiol 1979;293:393–415. (****)

Matthews G, Wickelgren WO. Glutamate and synaptic excitation of reticulospinal neurones of lamprey. J Physiol 1979;293:417–433. (****)

Nicholls DG. Proteins, transmitters and synapses. Oxford: Blackwell Scientific Publications, 1994. (**)

Wickman K, Clapham DE. Ion channel regulation by G proteins. Physiol Rev 1995;75:865–885. (***)

Chapter 9: Neural Control of Muscle Contraction

Huxley HE. A personal view of muscle and motility mechanisms. Ann Rev Physiol 1996;58:1–19. (**)

Rios E, Pizarro G, Stefani E. Charge movement and the nature of signal transduction in skeletal muscle excitation–contraction coupling. Ann Rev Physiol 1992;54:109–133. (***)

Schneider MF. Control of calcium release in functioning skeletal muscle fibers. Ann Rev Physiol 1994;56:463–484. (***)

Chapter 10: Spinal Cord Motor Mechanisms

Fetcho JR. The spinal motor system in early vertebrates and some of its evolutionary changes. Brain Behavior Evol 1992;40:82–97. (***)

Grillner S. Neural networks for vertebrate locomotion. Scientific American 1996;274:1, 64–69.(*)

Grillner S, Matsushima T. The neural network underlying locomotion in lamprey—synaptic and cellular mechanisms. Neuron 1991;7:1–15. (****)

Grillner S, Wallén P. Central pattern generators for locomotion, with special reference to vertebrates. Ann Rev Neuroscience 1985;8:233–261. (***)

Grillner S, Wallén P, Brodin L, Lansner A. Neuronal network generating locomotor behavior in lamprey: circuitry, transmitters, membrane properties, and simulation. Ann Rev Neuroscience 1991;14:169–199. (***)

Hagevik A, McClellan AD. Coupling of spinal locomotor networks in larval lamprey revealed by receptor blockers for inhibitory amino acids: neurophysiology and computer modeling. J Neurophysiol 1994;72:1810–1829. (****)

Jami L. Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. Physiol Rev 1992;72:623–666. (***)

McClellan AD, Jang W. Mechanosensory inputs to the central pattern generators for locomotion in the lamprey spinal cord: resetting, entrainment, and computer modeling. J Neurophysiol 1993;70:2442–2454. (****)

Pearson KG. Common principles of motor control in vertebrates and invertebrates. Ann Rev Neuroscience 1993;16:265–297. (***)

Chapter 11: Brain Motor Mechanisms

Albin RL, Young AB, Penney JB. The functional anatomy of disorders of the basal ganglia. Trends Neurosciences 1995;18:63–64. (**)

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neuroscience 1986;9:357–381. (***)

Evarts EV. Pyramidal tract activity associated with a conditioned hand movement in the monkey. J Neurophysiol 1966;29:1011–1027. (****)

Evarts EV. Relation of pyramidal tract activity to force exerted during voluntary movement. J Neurophysiol 1968;31:14–27. (****)

Georgopoulos AP. On reaching. Ann Rev Neuroscience 1986;9:147–170. (***)

Georgopoulos AP. Current issues in directional motor control. Trends Neuroscience 1995;18:506–510. (**)

Graybiel AM. The basal ganglia. Trends Neurosciences 1995;18:60–62. (**)

Talbott RE, Humphrey DR, eds. Posture and movement. New York: Raven Press, 1979. (****)

Thach WT, Goodkin HG, Keating JG. Cerebellum and adaptive coordination of movement. Ann Rev Neuroscience 1992;15:403–442. (***)

Wise SP. The primate premotor cortex: past, present, and preparatory. Ann Rev Neuroscience 1985;8:1–19. (***)

Wise SP, Strick PL. Anatomical and physiological organization of the non-primary motor cortex. Trends Neuroscience 1984;7:442–446. (**)

Chapter 12: Sensorimotor Integration

Andersen RA. Visual and eye movement functions of the posterior parietal cortex. Ann Rev Neuroscience 1989;12:377–403. (***)

Andersen RA, Brotchie PR, Mazzoni P. Evidence for the lateral intraparietal area as the parietal eye field. Curr Opinion Neurobiol 1992;2:840–846. (**)

Andersen RA, Gnadt JW. Posterior parietal cortex. In: Wurtz RH, Goldberg ME, eds. The neurobiology of saccadic eye movements. New York: Elsevier, 1989. (***)

Benson AJ. The vestibular sensory system. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:333–368. (***)

Buttner U, Fuhry L. Eye movements. Curr Opinion Neurol 1995;8:77–82. (**)

Dieterich M, Brandt T. Vestibulo-ocular reflex. Curr Opinion Neurol 1995; 8:83–88. (**)

Fuchs AF, Kaneko CRS, Scudder CA. (1985) Brainstem control of saccadic eye movements. Ann Rev Neuroscience 1985;8:307–337. (***)

Kornhuber HH, ed. Handbook of sensory physiology, vol VI/1. Vestibular system part 1: basic mechanisms. New York: Springer-Verlag, 1974. (***)

Leigh RJ, Brandt T. A reevaluation of the vestibulo-ocular reflex: new ideas of its purpose, properties, neural substrate, and disorders. Neurology 1993; 43:1288–1295. (****)

Leigh RJ, Zee DS. The neurology of eye movements, 2nd ed. Philadelphia: F.A. Davis, 1991. (***)

McIlwain JT. Distributed spatial coding in the superior colliculus: a review. Visual Neuroscience 1991;6:3–13. (***)

Sparks DL. Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. Physiol Rev 1986;66:118–171. (***)

Sparks DL, Barton EJ. Neural control of saccadic eye movements. Curr Opinion Neurobiol 1993;3:966–972. (**)

Sparks DL, Mays LE. Signal transformations required for the generation of saccadic eye movements. Ann Rev Neuroscience 1990;13:309–336. (***)

Chapter 13: The Autonomic Nervous System

Cabot JB. Some principles of the spinal organization of the sympathetic preganglionic outflow. Prog Brain Res 1995;107:29–42. (***)

Cabot JB. Sympathetic preganglionic neurons: cytoarchitecture, ultrastructure, and biophysical properties. In: Loewy AD, Spyer M, eds. Central Regulation of Autonomic Functions. New York: Oxford University Press, 1990:44–67. (****)

Campbell DL, Rasmusson RL, Strauss HC. Ionic current mechanisms generating vertebrate primary cardiac pacemaker activity at the single cell level: an integrative view. Ann Rev Physiol 1992;54:279–302. (***)

Clapham DE. Direct G protein activation of ion channels? Ann Rev Neuroscience 1994;17:441–464. (***)

Deal KK, England SK, Tamkun MM. Molecular physiology of cardiac potassium channels. Physiol Rev 1996;76:49–67. (***)

Elfvin L-G, Lindh B, Hökfelt T. The chemical neuroanatomy of sympathetic ganglia. Ann Rev Neuroscience 1993;16:471–507. (***)

Gilman AG. G proteins: transducers of receptor-generated signals. Ann Rev Biochem 1987;56:615–649. (***)

Hartzell HC. Regulation of cardiac ion channels by catecholamines, acetylcholine and second messenger systems. Prog Biophysics Molec Biol 1988;52:165–247. (***)

Hartzell HC, Méry P-F, Fischmeister R, Szabo G. Sympathetic regulation of cardiac calcium current is due exclusively to cAMP-dependent phosphorylation. Nature 1991;351:573–576. (****)

Irisawa H, Brown HF, Giles W. Cardiac pacemaking in the sinoatrial node. Physiol Rev 1993;73:197–227. (***)

Kobilka B. Adrenergic receptors as models for G protein-coupled receptors. Ann Rev Neuroscience 1992;15:87–114. (***)

Linder ME, Gilman AG. G proteins. Scientific American 1992;267:1, 56–61. (*)

Szabo G, Otero AS. G protein mediated regulation of K^+ channels in heart. Ann Rev Physiol 1990;52:293–305. (***)

Wickman K, Clapham DE. Ion channel regulation by G proteins. Physiol Rev 1995;75:865–885. (***)

Chapter 14: An Overview of Sensory Systems

Barlow HB. General principles: the senses considered as physical instruments. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:1–33. (***)

Iggo A. Cutaneous sensory mechanisms. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:369–408. (***)

McCormick DA, Bal T. (1994) Sensory gating mechanisms of the thalamus. Curr Opinion Neurobiol 1994;4:550–556. (**)

Spudich JL, Satir BH, eds. Sensory receptors and signal transduction. New York: Wiley-Liss, 1991. (***)

Chapter 15: The Somatic Senses

Gardner EP, Hamalainen HA, Palmer CI, Warren S. Touching the outside world: representation of motion and direction within primary somatosensory cortex. In: Lund JS, ed. Sensory processing in the mammalian brain: neural substrates and experimental strategies. New York: Oxford University Press, 1989:49–66. (****)

Hunt CC, ed. Handbook of sensory physiology, vol III/2. Muscle receptors. New York: Springer-Verlag, 1974. (***)

Iggo A. Cutaneous sensory mechanisms. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:369–408. (***)

Iggo A, ed. Handbook of sensory physiology, vol II. Somatosensory system. New York: Springer-Verlag, 1973. (***)

Iggo A, Andres KH. Morphology of cutaneous receptors. Ann Rev Neuroscience 1982;5:1–31. (***)

Kaas JH. What, if anything, is SI? Organization of first somatosensory area of cortex. Physiol Rev 1983;63:206–231. (***)

Lawson SN, Harper AA. Cell types in rat dorsal root ganglia: morphological, immunocytochemical, and electrophysiological analysis. In: Rowe M, Willis WD Jr, eds. Development, organization, and processing in somatosensory pathways. New York: Alan R. Liss, 1985:97–103. (****)

Willis WD, Coggeshall RE. Sensory mechanisms of the spinal cord. New York: Plenum Press, 1978. (****)

Chapter 16: The Visual System: Retina

Dowling JE. The retina. An approachable part of the brain. Cambridge, MA: Belknap Press, 1987. (**)

Euler T, Schneider H, Wässle H. Glutamate responses of bipolar cells in a slice preparation of the rat retina. J Neuroscience 1996;16:2934–2944. (****)

Finn JT, Grunwald ME, Yau KW. Cyclic nucleotide-gated ion channels—an extended family with diverse functions. Ann Rev Physiol 1996;58:395–426. (***)

Gilman AG. G proteins: transducers of receptor-generated signals. Ann Rev Biochem 1987;56:615–649. (***)

Hamm HE, Gilchrist A. Heterotrimeric G proteins. Curr Opinion Cell Biol 1996;8:189–196. (**)

Koutalos Y, Yau K-W. Regulation of sensitivity in vertebrate rod photoreceptors by calcium. Trends Neuroscience 1996;19:73–81. (**)

Lee BB. Receptive field structure in the primate retina. Vision Research 1996;36:631–644. (***)

Masland RH. The functional architecture of the retina. Scientific American 1986;255:6, 102–111. (*)

Nakanishi S. Second-order neurons and receptor mechanisms in visual- and olfactory-information processing. Trends Neuroscience 1995;18:359–364. (**)

Schnapf JL, Baylor DA. How photoreceptor cells respond to light. Scientific American 1987;256:4, 40–47. (*)

Wässle H, Boycott BB. Functional architecture of the mammalian retina. Physiol Rev 1991;71:447–480. (***)

Wu SM. Synaptic transmission in the outer retina. Ann Rev Physiol 1994;56:141–168. (***)

Yau K-W, Baylor DA. Cyclic GMP-activated conductance of retinal photoreceptor cells. Ann Rev Neuroscience 1989;12:289–327. (***)

Zagotta WN, Siegelbaum SA. Structure and function of cyclic nucleotide-gated channels. Ann Rev Neuroscience 1996;19:235–263. (***)

Zimmerman AL. Cyclic nucleotide gated channels. Curr Opinion Neurobiol 1995;5:296–303. (**)

Chapter 17: The Visual System: Higher Visual Processing

Das A. Orientation in visual cortex—a simple mechanism emerges. Neuron 1996;16:477–480. (***)

Deangelis GC, Ohzawa I, Freeman RD. Receptive field dynamics in the central visual pathways. Trends Neuroscience 1995;18:451–458. (**)

Katz LC, Callaway EM. Development of local circuits in mammalian visual cortex. Ann Rev Neuroscience 1992;15:31–56. (***)

Lund JS. Anatomical organization of macaque monkey striate visual cortex. Ann Rev Neuroscience 1988;11:253–288. (***)

Merigan WH, Maunsell JGR. How parallel are the primate visual pathways? Ann Rev Neuroscience 1993;16:369–402. (***)

Sherman SM. Dual response modes in lateral geniculate neurons—mechanisms and functions. Visual Neuroscience 1996;13:205–213. (****)

Somers DC, Nelson SB, Sur M. An emergent model of orientation selectivity in cat visual cortical simple cells. J Neuroscience 1995;15:5448–5465. (****)

Vidyasagar TP, Pei X, Volgushev M. Multiple mechanisms underlying the orientation selectivity of visual cortical neurones. Trends Neuroscience 1996;19:272–277. (**)

Willmer EN. Anatomy of the visual system. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:35–45. (***)

Zeki S. A vision of the brain. Oxford: Blackwell Scientific Publications, 1993. (**)

Chapter 18: Hearing and Other Vibration Senses

Ashmore JF. The electrophysiology of hair cells. Ann Rev Physiol 1991;53:465–476. (***)

Ashmore JF, Kolston PJ. Hair cell based amplification in the cochlea. Curr Opinion Neurobiol 1994;4:503–508. (**)

Benson AJ. The vestibular sensory system. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982:333–368. (***)

Corwin JT, Warchol ME. Auditory hair cells: structure, function, development, and regeneration. Ann Rev Neuroscience 1991;14:301–333. (***)

Evans EF. Functional anatomy of the auditory system. In: Barlow HB, Mollon JD, eds. The senses. Cambridge, UK: Cambridge University Press, 1982: 251–306. (***)

Gillespie PG. Molecular machinery of auditory and vestibular transduction. Curr Opinion Neurobiol 1995;5:449–455. (**)

Howard J, Roberts WM, Hudspeth AJ. Mechanoelectrical transduction by hair cells. Ann Rev Biophysics Biophysical Chem 1988;17:99–124. (***)

Keidel WD, Neff WD, eds. Handbook of sensory physiology, vol V/1. Auditory system. Anatomy and physiology (ear). New York: Springer-Verlag, 1974. (***)

Keidel WD, Neff WD, eds. Handbook of sensory physiology, vol V/2. Auditory system. Physiology (CNS). Behavioral studies. Psychoacoustics. New York: Springer-Verlag, 1975. (***)

Kornhuber HH, ed. Handbook of sensory physiology, vol VI/1. Vestibular system part 1: basic mechanisms. New York: Springer-Verlag, 1974. (***)

Mammano F, Ashmore JF. Reverse transduction measured in the isolated cochlea by laser Michelson interferometry. Nature 1993;365:838–841. (****)

Markin VS, Hudspeth AJ. (1995) Gating-spring models of mechanoelectrical transduction by hair cells of the internal ear. Ann Rev Biophysics Biomolec Struc 1995;24:59–83. (***)

Chapter 19: Chemical Senses

Beidler LM, ed. Handbook of sensory physiology, vol IV/1. Olfaction. New York: Springer-Verlag, 1971. (***)

Beidler LM, ed. Handbook of sensory physiology, vol IV/2. Taste. New York: Springer-Verlag, 1971. (***)

Bradley J, Li J, Davidson N, Lester HA, Zinn K. (1994) Heteromeric olfactory cyclic nucleotide-gated channels: a subunit that confers increased sensitivity to cAMP. Proc Natl Acad Sci USA 1994;91:8890–8894. (****)

Buck LB. (1996) Information coding in the vertebrate olfactory system. Ann Rev Neuroscience 1996;19:517–544. (***)

Crews L, Hunter D. (1994) Neurogenesis in the olfactory epithelium. Perspect Dev Neurobiol 1994;2:151–161. (****)

DeVries SH, Baylor DA. Synaptic circuitry of the retina and olfactory bulb. Cell 1993;72(suppl):139–149. (**)

Finn JT, Grunwald ME, Yau KW. Cyclic nucleotide-gated ion channels—an extended family with diverse functions. Ann Rev Physiol 1996;58:395–426. (***)

Firestein S. (1991) A noseful of odor receptors. Trends Neurosciences 1991; 14:270–272. (**)

Firestein S, Zufall F. The cyclic nucleotide gated channel of olfactory receptor neurons. Seminars Cell Biol 1994;5:39–46. (***)

Gilbertson TA, Avenet P, Kinnamon SC, Roper SD. Proton currents through amiloride-sensitive Na channels in hamster taste cells. J Gen Physiol 1992;100:803–824. (****)

Griff IC, Reed RR. The genetics of olfaction. Curr Opinion Neurobiol 1995; 5:456–460. (**)

Kinnamon SC. Taste transduction: a variety of mechanisms. Trends Neurosciences 1988;11:491–496. (**)

Kinnamon SC, Cummings TA. Chemosensory transduction mechanisms in taste. Ann Rev Physiol 1992;54:715–731. (***)

Kolesnikov SS, Margolskee RF. A cyclic-nucleotide–suppressible conductance activated by transducin in taste cells. Nature 1995;376:85–88. (****)

Margolskee RF. The biochemistry and molecular biology of taste transduction. Curr Opinion Neurobiol 1993;3:526–531. (**)

McLaughlin SK, McKinnon PJ, Margolskee RF. Gustducin is a taste-cell–specific G protein closely related to the transducins. Nature 1992;357:563–569. (****)

McLaughlin S, Margolskee RF. The sense of taste. Am Scientist 1994;82:538–545. (*)

Nakanishi S. Second-order neurons and receptor mechanisms in visual- and olfactory-information processing. Trends Neuroscience 1995;18:359–364. (**)

Reed RR. Signaling pathways in odorant detection. Neuron 1992;8:201–209. (***)

Roper SD. The cell biology of vertebrate taste receptors. Ann Rev Neuroscience 1989;12:329–353. (***)

Ruiz-Avila L, McLaughlin SK, Wildman D, McKinnon PJ, Robichon A, Spickofsky N, Margolskee RF. Coupling of bitter receptor to phosphodiesterase through transducin in taste receptor cells. Nature 1995;376:80–85. (****)

Zagotta WN, Siegelbaum SA. Structure and function of cyclic nucleotide-gated channels. Ann Rev Neuroscience 1996;19:235–263. (***)

Zufall F, Firestein S, Shepherd GM. Cyclic nucleotide-gated ion channels and sensory transduction in olfactory receptor neurons. Ann Rev Biophysics Biomolec Struc 1994;23:577–607. (***)

Chapter 20: Neural Development

Apel E, Merlie J. Assembly of the postsynaptic apparatus. Curr Opinion Neurobiol 1995;5:62–67. (**)

Bentley D, O'Connor TP. Cytoskeletal events in growth cone steering. Curr Opinion Neurobiol 1994;4:43–48. (**)

Brown A, Slaughter T, Black MM. Newly assembled microtubules are concentrated in the proximal and distal regions of growing axons. J Cell Biol 1992;119:867–882. (****)

Chu GC, Moscoso LM, Sliwkowski MX, Merlie JP. Regulation of the acetylcholine receptor epsilon subunit gene by recombinant ARIA: an in vitro model for transynaptic gene regulation. Neuron 1995;14:329–339. (****)

Colamarino SA, Tessier-Lavigne M. The role of the floor plate in axon guidance. Ann Rev Neuroscience 1995;18:497–529. (***)

Connor EA, Smith MA. Retrograde signaling in the formation and maintenance of the neuromuscular junction. J Neurobiol 1994;25:722–739. (****)

Doherty P, Walsh FS. Signal transduction events underlying neurite outgrowth stimulated by cell adhesion molecules. Curr Opinion Neurobiol 1994; 4:49–55. (**)

Duclert A, Changeux JP. Acetylcholine receptor gene expression at the developing neuromuscular junction. Physiol Rev 1995;75:339–368. (***)

Fallon JR, Hall ZW. Building synapses: agrin and dystroglycan stick together. Trends Neurosciences 1994;17:469–473. (**)

Fantl WJ, Johnson DE, Williams LT. Signalling by receptor tyrosine kinases. Ann Rev Biochem 1993;62:453–481. (***)

Fukui A, Asashima M. Control of cell differentiation and morphogenesis in amphibian development. Intl J Develop Biol 1994;38:257–266. (****)

Goodearl AD, Yee AG, Sandrock AW Jr, Corfas G, Fischbach GD. ARIA is concentrated in the synaptic basal lamina of the developing chick neuromuscular junction. J Cell Biol 1995;130:1423–1434. (****)

Goodman CS. Mechanisms and molecules that control growth cone guidance. Ann Rev Neuroscience 1996;19:341–377. (***)

Harland RM. Neural induction in *Xenopus*. Curr Opinion Genetics Develop 1994;4:543–549. (**)

Hatten ME. The role of migration in central nervous system neuronal development. Curr Opinion Neurobiol 1993;3:38–44. (**)

Hatten ME, Heintz N. Mechanisms of neural patterning and specification in the developing cerebellum. Ann Rev Neuroscience 1995;18:385–408. (***)

Hemmati-Brivanlou A, Kelly OG, Melton D. Follistatin, an antagonist of activin, is expressed in the Spemann organizer and displays direct neuralizing activity. Cell 1994;77:283–295. (****)

Jacobson M. Clonal analysis and cell lineages of the vertebrate central nervous system. Ann Rev Neuroscience 1985;8:71–102. (***)

Keegan K, Halegoua S. Signal transduction pathways in neuronal differentiation. Curr Opinion Neurobiol 1993;3:14–19. (**)

Kessler DS, Melton D. Vertebrate embryonic induction: mesodermal and neural patterning. Science 1994;266:596–602. (**)

Kintner C. Molecular basis of early neural development in *Xenopus* embryos. Ann Rev Neuroscience 1992;15:251–284. (***)

Knecht AK, Good PJ, Dawid IB, Harland RM. Dorsal–ventral patterning and differentiation of noggin-induced neural tissue in the absence of mesoderm. Development 1995;121:1927–1935. (****)

Kuhn TB, Schmidt MF, Kater SB. Laminin and fibronectin guideposts signal sustained but opposite effects to passing growth cones. Neuron 1995;14:275–285. (****)

Lamb TM, Knecht AK, Smith WC, Stachel SE, Economides AN, Stahl N, Yancopolous GD, Harland RM. Neural induction by the secreted polypeptide noggin. Science 1993;262:713–718. (**)

Levi-Montalcini R, Angeletti PU. Nerve growth factor. Physiol Rev 1968; 48:534–569. (**)

Luo Y, Raper JA. Inhibitory factors controlling growth cone motility and guidance. Curr Opinion Neurobiol 1994;4:648–654. (**)

Mandel G, McKinnon D. Molecular basis of neural-specific gene expression. Ann Rev Neuroscience 1993;16:323–345. (***)

McMahan UJ. The agrin hypothesis. Cold Spring Harbor Symposia on Quantitative Biology 1990;55:407–418. (***)

Meier T, Perez GM, Wallace BG. Immobilization of nicotinic acetylcholine receptors in mouse C2 myotubes by agrin-induced protein tyrosine phosphorylation. J Cell Biol 1995;131:441–451. (****)

Puschel AW, Adams RH, Betz H. Murine semaphorin D/collapsin is a member of a diverse gene family and creates domains inhibitory for axonal extension. Neuron 1995;14:941–948. (****)

Sandrock AW Jr, Goodearl AD, Yin QW, Chang D, Fischbach GD. ARIA is concentrated in nerve terminals of neuromuscular junctions and at other synapses. J Neuroscience 1995;15:6124–6136. (****)

Sanes JR. Extracellular matrix molecules that influence neural development. Ann Rev Neuroscience 1989;12:491–516. (***)

Schwab ME, Kapfhammer JP, Bandtlow CE. Inhibitors of neurite growth. Ann Rev Neuroscience 1993;16:565–595. (***)

Slack JM. Inducing factors in *Xenopus* early embryos. Curr Biol 1994;4:116–126. (**)

Thomsen G, Wolf T, Whitman M, Sokol S, Vaughn J, Vale W, Melton D. Activins are expressed early in *Xenopus* embryogenesis and can induce axial mesoderm and anterior structures. Cell 1990;63:485–493. (****)

Treisman R. Regulation of transcription by MAP kinase cascades. Curr Opinion Cell Biol 1996;8:205–215. (**)

van der Geer P, Hunter T, Lindberg RA. Receptor protein-tyrosine kinases and their signal transduction pathways. Ann Rev Cell Biol 1994;10:251–337. (***)

Wallace BG. Regulation of the interaction of nicotinic acetylcholine receptors with the cytoskeleton by agrin-activated protein tyrosine kinase. J Cell Biol 1995;128:1121–1129. (****)

Chapter 21: Synaptic Plasticity

Arancio O, Kandel ER, Hawkins RD. Activity-dependent long-term enhancement of transmitter release by presynaptic 3′,5′-cyclic GMP in cultured hippocampal neurons. Nature 1995;376:74–80. (****)

Artola A, Singer W. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosciences 1993;16:480–487. (**)

Bailey CH, Kandel ER. Structural changes accompanying memory storage. Ann Rev Physiol 1993;55:397–426. (***)

Bear MF, Abraham WC. Long-term depression in hippocampus. Ann Rev Neuroscience 1996;19:437–462. (***)

Bredt DS, Snyder SH. Nitric oxide: a physiologic messenger molecule. Ann Rev Biochem 1994;63:175–195. (***)

Byrne JH, Kandel ER. Presynaptic facilitation revisited: state and time dependence. J Neuroscience 1996;16:425–435. (**)

Chain DG, Hegde AN, Yamamoto N, Liu-Marsh B, Schwartz JH. Persistent activation of cAMP-dependent protein kinase by regulated proteolysis suggests a neuron-specific function of the ubiquitin system in *Aplysia*. J Neuroscience 1995;15:7592–7603. (****)

Collingridge GL, Bliss TVP. Memories of NMDA receptors and LTP. Trends Neurosciences 1995;18:54–56. (**)

Davis RL. Physiology and biochemistry of *Drosophila* learning mutants. Physiol Rev 1996;76:299–317. (***)

Delaney KR, Tank DW. A quantitative measurement of the dependence of short-term synaptic enhancement on presynaptic residual calcium. J Neuroscience 1994;14:5885–5902. (****)

du Lac S, Raymond JL, Sejnowski TJ, Lisberger SG. Learning and memory in the vestibulo-ocular reflex. Ann Rev Neuroscience 1995;18:409–441. (***)

Garthwaite J. Neural nitric oxide signalling. Trends Neurosciences 1995;18:51–52. (**)

Gustafsson B, Wigstrom H, Abraham WC, Huang YY. Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. J Neuroscience 1987;7:774–780. (****)

Hawkins RD, Kandel ER, Siegelbaum SA. Learning to modulate transmitter release: themes and variations in synaptic plasticity. Ann Rev Neuroscience 1993;16:625–665. (***)

Kaang BK, Kandel ER, Grant SG. Activation of cAMP-responsive genes by stimuli that produce long-term facilitation in *Aplysia* sensory neurons. Neuron 1993;10:427–435. (****)

Larkman AU, Jack JJB. Synaptic plasticity: hippocampal LTP. Curr Opinion Neurobiol 1995;5:324–334. (**)

Linden DJ, Connor JA. Long-term synaptic depression. Ann Rev Neuroscience 1995;18:319–357. (***)

Nicoll RA, Malenka RC. Contrasting properties of two forms of long-term potentiation in the hippocampus. Nature 1995;377:115–118. (***)

Raymond JL, Lisberger SG, Mauk MD. The cerebellum: a neuronal learning machine? Science 1996;272:1126–1131. (**)

Ruegg MA. Agrin, laminin beta-2 (S-laminin) and ARIA—their role in neuromuscular development. Curr Opinion Neurobiol 1996;6:97–103. (**)

Schuman EM, Madison DV. Nitric oxide and synaptic function. Ann Rev Neuroscience 1994;17:153–183. (***)

Stirling RV, Dunlop SA. The dance of the growth cones—where to next? Trends Neurosciences 1995;18:111–115. (**)

Tanaka C, Nishizuka Y. The protein kinase C family for neuronal signaling. Ann Rev Neuroscience 1994;17:551–567. (***)

Yin JCP, Tully T. CREB and the formation of long-term memory. Curr Opinion Neurobiol 1996;6:264–268. (**)

Zhang J, Snyder SH. Nitric oxide in the nervous system. Ann Rev Pharmacol Toxicol 1995;35:213–233. (***)

Zucker RS. Short-term synaptic plasticity. Ann Rev Neuroscience 1989;12:13–31. (***)

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